Dose-escalation Study of a Contrast Agent for Delineation of Urological Anatomy in Minimally Invasive Surgery

Protocol LICOR-10417-01

NCT03106038

A Phase I/IIa dose-escalation study to evaluate the use of an investigational imaging agent for the detection of urologic anatomy via near-infrared fluorescence imaging in the setting of minimally invasive surgery

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PROTOCOL APPROVAL PAGE

Protocol Number:	**LICOR-10417-01**
Version:	**4.0**
Date:	**09 FEB 2018**

We, the undersigned, have reviewed this protocol and agree that it contains all relevant information required to meet FDA, GCP and all applicable regulatory guidelines and statutes.

PROTOCOL APPROVAL FOR USE

Polly Harris LI-COR, Inc. Director, Quality Assurance	Date
Joy Kovar LI-COR, Inc. Principal Scientist	Date
Vassil Elitzin LI-COR, Inc. Director CMC	Date
Greg Biggs LI-COR, Inc. Chief Executive Officer	Date

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**LICOR-10417-01**
Version:	**4.0**
Date:	**19 FEB 2018**

I have read the protocol specified above and agree to participate in and comply with the procedures as outlined herein for the conduct of this clinical trial. I also agree to comply with US Food and Drug Administration (FDA) regulations and Investigational Review Board/Institutional Ethics (IRB/IEC) requirements for testing on human subjects. I agree to ensure that the requirements for obtaining informed consent are met.

Principal Investigator's Signature _____ Date _____

Kenneth Kim, MD

Site Number: **01**

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PROTOCOL SYNOPSIS

Name of Sponsor/Company: LI-COR, Inc.	
Name of Study Product: IRDye™ 800BK Injection	
Protocol Number: LICOR-10417-01	**Indication:** Detection of pelvic urologic anatomy in female subjects undergoing minimally invasive surgery.
Title of Study: A Phase I/IIa, dose-escalation study to evaluate the use of an investigational imaging agent for the detection of urologic anatomy via near-infrared fluorescence imaging in the setting of minimally invasive surgery.	
Study Center: University of Alabama at Birmingham	
Planned Number of Subjects: Estimated 48 female subjects	**Study Development Phase:** I/IIa
Indication for Use: Detection of pelvic urologic anatomy in female subjects undergoing minimally invasive surgery.	

Name of Sponsor/Company: LI-COR, Inc.	
Name of Study Product: IRDye™ 800BK Injection	
Protocol Number: LICOR-10417-01	**Indication:** Detection of pelvic urologic anatomy in female subjects undergoing minimally invasive surgery.

Objectives:

Version 4 of this protocol tranforms this study design into 2 parts; Part A is the original, up through Version 3, protocol for dose optimalization. Part B adds 2 cohorts of subjects to be tested with multiple imaging devices using the near optimal dose found in Part A.

The objectives of Part A of this study are:

- To determine the safety of IRDye 800BK Injection in the detection of pelvic urologic anatomy, particularly the ureter, via near-infrared fluorescence imaging in female subjects undergoing minimally invasive surgery.
- To determine the efficacy of IRDye 800BK Injection for the detection of pelvic urologic anatomy, particularly the ureter, via near-infrared fluorescence imaging in female subjects undergoing minimally invasive surgery.
- To assess the dose response and determine the timing interval for the detection of pelvic urologic anatomy, particularly the ureter, via near-infrared fluorescence imaging in female subjects undergoing minimally invasive surgery.

The objective of Part B of this study is:

- To verify that the image efficacy of the near optimal dose determined in Part A is similar when using a selection of commercially available endoscopic imaging systems . The systems selected for evaluation are :
  1) da Vinci Firefly Fluorescence Imaging System from Intuitive Surgical, Inc.
  2) PINPOINT Endoscopic Fluorescence Imaging System (Novadaq, Mississauga, Ontario, CANADA) and
  3) Stryker Infrared Illuminating System (IRIS) [AIM light source] (Stryker, Kalamazoo, MI USA).

Study Design

This is a single site, 2-part, Phase I/IIa, dose-escalation study evaluating the use of IRDye 800BK Injection to detect urologic structures, particularly the ureter, with NIRF imaging, in women undergoing minimally invasive pelvic surgery. The safety and efficacy of IRDye 800BK Injection will be assessed after each dose cohort. There will be two Parts to this study. The objective of Part A is to determine safety of the dye and the near optimal dose based on a dose escalation/de-escalation study using the da Vinci Firefly imaging device. The objective of Part B is to show that similar imaging scores can be obtained with a selection of commercially-available medical imaging devices. There will be at least eight (8) subjects per cohort for Part A. Part B will have at least 16 subjects, with at least 8 subjects assessed with the da Vinci Firefly Imaging System concurrent with the Novadaq PINPOINT Endoscopic Fluorescence Imaging System device, and at least 8 subjects assessed with the da Vinci Firefly Imaging System concurrent with the Stryker Infrared Illuminating System (IRIS) [AIM light source].

Study Outcomes (Endpoints):

Safety Outcome Measures

The safety outcome measurements for the study will be primarily assessed by:

- Evaluation of injection site reactions
- Incidence of Treatment-Emergent Serious Adverse Events (TESAE)
- Incidence of Treatment-Emergent Adverse Events (TEAE)
- Incidence of unanticipated adverse device effects (UADEs) related to imaging devices
- Incidence of withdrawals from the study due to TEAEs and/or UADEs
- Changes and shifts in laboratory measurements over time

Efficacy Outcome Measures

Part A: The efficacy outcomes for Part A of the study are primarily assessed by the dose response based on a composite assessment of the anatomy and laterality for detection of the pelvic ureter in women undergoing minimally invasive surgery. This outcome is measured by the composite scales from the following ureteral imaging scales with 0 being the worst and 4 being the best:

i) Anatomy:	Entire ureter length from pelvic brim down (2); Partial length (1); or No signal visualized (0).
ii) Laterality:	Bilateral (2); Right ureter only or Left ureter only (1); or None (0).

- Ureter visualization, by dose, over time post-infusion from 10 minutes through 90 minutes
- Anatomical detection of pelvic ureter using ureteral imaging scales (i.e., the entire ureter length from pelvic brim down, partial length, or no signal visualized).
- Lateral detection of pelvic ureter using ureteral imaging scales (i.e., bilateral, right or left ureter only, or none).

Part B: The efficacy outcome for Part B is based on the visualization/detection of the pelvic ureter using other selected FDA cleared imaging devices to obtain the composite assessment described above at the single optimal dose level. The surgery will be conducted using the daVinci robotic system using the Firefly Imaging System. At 10 and 30 minutes post-injection, images will be captured by two devices where one cohort of patients (cohort 4) will have images captured by the da Vinci Firefly Imaging System and the Pinpoint Endoscopic Fluorescence Imaging System, and the other cohort (cohort 5) will have images captured by the da Vinci Firefly Imaging System and the Stryker Infrared Illuminating System device. While the images will not be collected simultaneously, the images will be collected within approximately one minute of each other. The ureteral imaging scores will be collected to assess in real time, within subjects, the images obtained from the Pinpoint Endoscopic Fluorescence Imaging System and the Stryker Infrared Illuminating System against the da Vinci Firefly Imaging System.

Trial Design:

This is a single site, 2 part, Phase I/IIa, dose-escalation study evaluating the use of IRDye™ 800BK Injection to detect urologic structures, particularly the ureter, with near-infrared fluorescence (NIRF) imaging, in women undergoing minimally invasive pelvic surgery. All surgeries for this study will be conducted using the Firefly™ Fluorescence Imaging System from Intuitive Surgical, Inc. as the imaging device. Part A of the study will determine the near-optimal dose by comparing the ureteral images obtained with varying doses of IRDye 800BK for Injection. Once the near optimal dose has been determined in Part A of the study, the ureter image will also be assessed in two new cohorts of subjects using the PINPOINT Endoscopic Fluorescence Imaging System (Novadaq, Mississauga, Ontario, CANADA) or the Stryker Infrared Illuminating System (IRIS) [AIM light source] (Stryker, Kalamazoo, MI USA) in Part B of the study.

All of the imaging systems used in this protocol are FDA-cleared medical device imagers indicated for real-time endoscopic visible and NIRF imaging in minimally invasive surgeries. It is not anticipated that the use of an additional imaging device during the procedure will extend the procedure or cause additional risk for the subjects. These surgeries follow the standard of care with the da Vinci robotic surgical system with the Firefly Fluorescence Imaging system. Four to five ports are used for these surgeries. One of these ports is used as an accessory port, and the additional imaging device (i.e., endoscope) will be introduced in this standard accessory port. No additional incisions/ports will be required to use these other imaging devices. The standard of care for these patients will not be altered based on the images obtained under this protocol. This additional imaging should take two minutes at the most and as such, will not prolong the surgery significantly. The NIR camera systems and their usage in the protocol are proposed to be non-significant risk (NSR) as they do not meet the criteria of a significant risk device defined in 21CFR 812.3. See Appendix 2.

Duration of Treatment: 90 minutes or less

Inclusion Criteria: Subjects are required to meet all of the following criteria for enrollment into the study:

1. Provide written informed consent prior to the initiation of study procedures.
2. Are > 18 years of age.
3. Women consented to undergo standard of care minimally invasive pelvic surgery (traditional laparoscopy and robotic surgery).
4. Women who are expected to be admitted to the hospital following surgery for at least 24 hours.

Exclusion Criteria: Subjects meeting any of the following criteria will be excluded from enrollment:

1. Are unwilling or unable to provide informed consent.
2. Are unwilling or unable to comply with the requirements of the protocol.
3. History of prior urologic surgery.
4. History of prior pelvic surgery.
5. History of known retroperitoneal fibrosis.
6. Have any of the following screening laboratory values:
    a. Hemoglobin ≤ 8.0 g/dL
    b. Absolute neutrophil count (ANC) ≤ 1500/µL
    c. Platelet count ≤ 100,000/µL
    d. Serum creatinine ≥ 1.5 x the institutional upper limit of normal (IULN) creatinine
    e. Serum bilirubin ≥ 1.5 x IULN
    f. Aspartate transaminase (AST or serum glutamic oxaloacetic transaminase, SGOT) ≥ 2x IULN
    g. Alanine transaminase (ALT or serum glutamate pyruvate transaminase, SGPT) ≥ 2 x IULN
7. Females who are pregnant, lactating, or breastfeeding.
8. Patients having undergone a sentinel lymph node biopsy.
9. Any other condition that, in the Investigator's judgment, would potentially compromise the study compliance or the ability to evaluate safety or efficacy.

Study Procedures:

There will be a total of five (5) visits for this study. These 5 visits are consistent for Part A and Part B of the study. The procedures are as follows:

Screening Visit (1): After signing the informed consent form, the subject will have a history and full physical exam, height and weight measured, vital signs including temperature, electrocardiogram (ECG), assessment of baseline medications, and routine laboratory assessments including a urine pregnancy test and urinalysis. The history and physical exam may be performed, at the investigator's discretion, during the pre-operative visit.

Within 24 hours prior to the surgical procedure and administration of the imaging product, the investigator will review all the laboratory and examination results. If the subject qualifies for the study, a phone call

will be made, and it will be documented that the subject is aware of her qualification and still wishes to continue with the study.

Pre-operative Visit (2.1): On the morning of surgery, the subject will be assigned a treatment number and the infusion dye will be mixed according to her pre-operative weight on the day of surgery. A pregnancy test and vital signs will be performed. Concomitant medications will be reviewed.

Intraoperative Visit (2.2): The subject will receive IRDye 800BK Injection solution intravenously.

(Part A): Vital signs, image reading assessments, and an injection site assessment will be recorded at 10, 20, 30, 45, 60, 75 and 90 minutes (± 5 minutes) post-infusion.

(Part B): Vital signs, image reading assessments, and an injection site assessment will be recorded at 10 and 30 minutes (± 5 minutes) post-infusion.

Any adverse events or additional medications will be recorded for both Parts A & B.

Post-Operative Visit (3): Within 12 hours post-surgery, the subject will have routine blood labs, urinalysis, vital signs, and assessment of medication changes. In addition, an ECG and assessment of adverse events will be performed.

Post-Operative Visit (4): Twenty-four hours post-surgery, the subject will have routine blood labs, urinalysis, vital signs, ECG, full physical exam, and an assessment of adverse events and changes to medication.

Follow-Up Check (5): At 28 days post-surgery, the subject will return for a post-operative follow up. At this time study personnel will ascertain if any adverse events occurred.

Statistical Considerations:

Sample Size Determination and Rationale

Sample Size: An estimated 48 subjects, eight (8) per cohort, may be enrolled in this trial. The original sample size calculation for this study (N=32) was based on clinical judgment that there will be a large, e.g. at least 70% clinically meaningful difference between the visualization of the highest dose of IRDye 800BK, and the lowest dose. In addition, because the treatment is a single surgical procedure, drop outs are not expected in the study. An additional 16 subjects will be enrolled into Part B, 8 per pairing of imaging devices (da Vinci Firefly vs Novadaq PINPOINT; da Vinci Firefly vs Stryker AIM) to be consistent with the cohorts in Part A. No statistical rationale was used to determine this sample size.

Efficacy Analyses

The analyses of efficacy outcomes will be conducted on the Intent to Treat (ITT) and Efficacy Evaluable (EE) populations, if different from the ITT population.

The efficacy analyses for the study Part A, including the dose-response relationships and trend analyses, will be conducted using the appropriate statistical test on the composite assessment of the anatomy and laterality data of the ureter. In addition to the trend analysis for the composite outcome, the data will also be compared between the dose groups using analysis of covariance (ANCOVA). For all other efficacy outcomes, the data will be summarized and compared according to the variable type:

- Continuous data summaries will include:
  - Descriptive summary of number of observations, mean, standard deviation, median, and minimum and maximum values
  - (ANCOVA) for inferential statistics
- Categorical data summaries will include:
  - Frequency counts and percentages
  - Logit model for inferential statistics

The evaluation of images from the different devices obtained in Part B of the study is being used to explore the degree of concordance of the image scores produced from the selected imaging devices in real time within the same subject. Part B has not been powered to explore the differences between imaging devices. Subjects in cohort 4 (Firefly and PINPOINT) will be scored for the frequency in agreement of composite image scores from each device. Likewise, cohort 5 (Firefly and Stryker) will be scored.

Safety assessments

Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment emergent adverse events (TEAE) are defined as events with an onset on or after the administration of the treatment. TEAEs will be summarized by dose group, System Organ Class (SOC), and preferred term. The following TEAE summaries will be provided:

- TEAEs by severity grade
- TEAEs by relationship to study treatment

In addition:

- Injection site reactions will be summarized
- The frequency of adverse events will be summarized
- Separate summaries of imaging device-related adverse events, including UADEs
- Adverse events resulting in discontinuation of study treatment will be presented

Withdrawal rules have been defined as followed:

- Occurrence of an anaphylactic or other significant allergic reaction to IRDye 800BK Injection.
- Ongoing clinical adverse event related to the IRDye 800BK Injection.
- Occurrence of an SAE related to IRDye 800BK Injection.
- Occurrence of an UADE related to the imaging device.
- A subject is significantly non-compliant with the requirements of the protocol.
- The investigator determines that it is in the best interest of the subject.
- Subject chooses to withdraw or is withdrawn due to an adverse event.
- Discontinuation of the study by the Sponsor.
- Subject withdrew consent.

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List of Abbreviations

Abbreviation	Term
AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ANCOVA	Analysis of Covariance
AST	Aspartate transaminase
AUC	Area under the plasma concentration time curve
AUC_{last}	Last measurable concentration
BMI	Basal metabolic index
BUN	Blood urea nitrogen
C_0	Concentration at time “0”
CBC	Complete blood count
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically significant
dL	Deciliter
DMF	Dimethylformamide
DSMC	Data Safety Monitoring Committee
DSMO	Dimethylsulfoxide
EE	Efficacy evaluable population
eCRF	Electronic case report form
ECG	Electrocardiogram
FDA	U.S. Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hct	Hematocrit
HEENT	Head, ears, eyes, nose, and throat
HIPAA	Health Insurance Portability Accountability Act
IA	Interim analysis
ICF	Informed consent form
ICH	International Conference on Harmonization

Abbreviation	Term
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent to treat population
IULN	Institutional upper limit of normal
IV	Intravenous
Kg	Kilogram
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
µL	Microliter
Mg	Milligram
mL	Milliliter
N	Number in sample
NCS	Not clinically significant
NIRF	Near-infrared fluorescence
Nm	Nanometer
NOAEL	No Observed Adverse Effect Level
PBS	Phosphate Buffered Saline
PI	Principal Investigator
PK	Pharmacokinetics
PT	Prothrombin time
PTT	Partial prothrombin time
®	Registered Trademark
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamate pyruvate transaminase
SOC	System Organ Class
SOP	Standard Operating Procedure
SV	Screening visit

Abbreviation	Term
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TM	Trademark
UADE	Unanticipated Adverse Device Effect
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND

1.1. STATEMENT OF INTENT

The design, conduct and reporting of this study shall be conducted in compliance with the protocol, International Conference on Harmonization/Good Clinical Practice (ICH/GCP), and all appropriate regulatory requirements. Investigator(s) participating in this study will have documented training in GCP. Independent monitoring of the trial will be accomplished utilizing a Contract Research Organization (CRO).

1.2. BACKGROUND OF THE DISEASE

Injuries to the urinary tract can happen either during surgery (iatrogenic) or following trauma to the lower abdomen. The impact of acute urinary tract injuries, when not recognized immediately, is potentially life-threatening and can result in permanent kidney damage or removal (Brandes, 2011). Iatrogenic bladder injuries are the most frequent urologic injury, but they are usually recognized and repaired immediately, and potential complications are typically minor (Brandes, 2011). In contrast, 50-70% of iatrogenic ureteral injuries are diagnosed postoperatively (Burks and Santucci, 2014)(Ostrzenski, Radolinski, and Ostrzenska, 2003). Gynecological surgery accounts for 52–82% of iatrogenic injuries (Burks and Santucci, 2014). The rate of injury is approximately 0.5 to 2% of all hysterectomies and routine gynecologic pelvic operations, with injury following radical hysterectomies being historically more frequent, averaging 10% (with a range of 5 to 30%), although this incidence appears to have declined recently owing to improved patient selection and surgical procedures (Brandes, 2011)(McGeady and Breyer, 2013). The lack of tactile methods in robotic and laparoscopic procedures combined with surgeons' failure to properly locate the ureters have previously been associated with increasing rates of inadvertent ureteral injuries across various surgical specialties (Saidi et al., 1996). Indeed, although higher rates of intraoperative complications were found to occur in open abdominal approaches (abdominal total and supracervical hysterectomy) compared to minimally invasive approaches (laparoscopic and robotic), when the data were analyzed by injury type, higher rates of ureteral injury were seen in the post-robotic (11.4%, n = 5) compared to the pre-robotic period (2.4%, n = 1, p = 0.05) (Rahimi, et al., 2014). The most reliable way for surgeons to avoid ureteral injury is to clearly identify the ureter during surgery (Brandes, 2011). Although a surgeon's clinical acumen and technical ability remain paramount, certain imaging technologies can augment the surgeon's ability to visualize specific structures which can improve surgical techniques and outcomes (Hsu et al., 2014). Currently available technologies, such as preoperative ureteral radiographic imaging or placement of an illuminating stent, have not been widely adopted either because they are often not particularly helpful during surgery, or they are unnecessarily cumbersome for use in low risk surgery. By enabling a dynamic recognition of anatomic landmarks, the use of an imaging agent like IRDye

800BK should increase the efficiency of pelvic/abdominal surgeries and may lead to a reduction in operative time. Use of IRDye 800BK may also lead to a reduction in the incidence of morbidities and complications related to prolonged general anesthesia. Resource savings would also be expected to accrue from the obviation of salvage surgeries.

1.3. NAME AND DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

The name of the investigational product used in this study is IRDye 800BK Injection. By enabling a dynamic recognition of anatomic landmarks, the use of IRDye 800BK Injection should increase the efficiency of pelvic/abdominal surgeries and lead to a reduction in operative time and the associated operating room costs. Use of the dye should also lead to a reduction in the incidence of morbidities and complications related to prolonged general anesthesia. Resource savings would also be expected to accrue from the obviation of salvage surgeries. IRDye 800BK is a near-infrared imaging agent that is intended to be used as a surgical aid to visualize ureters and the bladder and allow their structural delineation during pelvic or abdominal surgery.

IRDye 800BK Injection will be systemically administered to surgical patients through intravenous injection. Clear identification of ureters is often very difficult to do but remains essential in order to avoid inadvertent ureteral injury. Optimal optical imaging occurs in the near-infrared region due to the spectrum's excellent biological tissue penetration, favorable signal-to-background ratio owing to minimal auto-fluorescence from biological samples/tissues, and minimized scattering and absorption effects. Near-infrared light also exerts minimal photo-damage to biological samples/tissues (Guo et. al., 2014). Because the human eye is insensitive to near-infrared wavelengths, the use of imaging agents such as IRDye 800BK provides significant practical advantages during surgery as they do not alter the surgical field.

Use of IRDye 800BK requires a fluorescent imaging device with compatible excitation and emission wavelengths. In this study, ureters will be visualized using near-infrared fluorescence camera systems at an excitation of 750-810 nm and an emission wavelength of 800-850 nm. Imaging instruments that operate within this spectral range would be expected to be compatible with IRDye 800BK. Therefore, there are multiple appropriate FDA-cleared surgical imaging agents other than IRDye 800BK, e.g., Firefly™ Fluorescence Imaging System, Stryker AIM Fluorescence Imaging System, and Novadaq PINPOINT Fluorescence Imaging System.

1.4. PRE-CLINICAL STUDIES

Preclinical studies assessing safety, toxicity, and mutagenicity have been conducted to generate supporting evidence/data for the use of IRDye 800BK as an imaging agent.

1.4.1 Intraoperative fluorescent imaging of the porcine genitourinary system with IRDye 800BK

Two exploratory studies have been conducted in the pig model, which was chosen because of its anatomical similarity to humans. Commercially available near-infrared fluorescence laparoscopy imaging systems such as Karl Storz™ (Germany) or the PINPOINT Endoscopic Fluorescence Imaging System™ system from Novadaq (Canada) were used to visualize the dye intraoperatively. The surgical operations were laparoscopically assisted and conducted under general anesthesia.

In one study, three doses (0.077, 0.154 and 0.3 mg/kg) were administered in intravenous boluses directly after introduction of the laparoscopic trocars. For these studies, IRDye™ 800BK was dissolved in phosphate buffered saline (PBS) at a concentration of 1 mg/mL. At the lowest dose tested (0.077 mg/kg) both left and right ureters were visible at the 20-minute time-point, and remained so until the end of the experiment after 120 minutes. For all doses, maximal fluorescence signal intensity (which increased with dose) was seen during the peristaltic contractions of the ureter that showed the transport of the intra-luminal urine from proximal to distal sections of the ureter. No clinically relevant changes in vital parameters were observed at any test dose.

In the second dose study, four doses (0.03, 0.06, 0.09, and 0.120 mg/kg) with 3 pigs per dose were evaluated for visualization of the ureters using the Novadaq imaging system (standard instrument settings). The pelvic ureter was identified in all 12 pigs. Time to identify ureter via fluorescence imaging was directly dependent on the dose given (i.e., shorter time to identification with increasing doses of IRDye 800BK). Of note, in 10/12 of pigs, some portion of the ureter was seen by 20 minutes. Full visualization of the ureter was seen starting at a 0.06 mg/kg dose with optimal and consistent visualization at 0.09 and 0.120 mg/kg doses. Based on qualitative visualization, the optimal dose for future clinical trials was determined to be 0.09 mg/kg. This dose was selected based on three factors: time to visualize, visualization of the entire pelvic ureter, and strength of signal. There were no observed physiologic or adverse events documented after administration of IRDye 800BK during the 60-minutes observation period.

1.4.2 Dose Range-Finding Toxicity Study of IRDye 800BK Administered by Intravenous Injection to Rats

The objective of this study was to determine the potential for toxicity of IRDye 800BK when it was administered as a single intravenous injection to rats. Male (n=24) and female (n=24) Sprague Dawley rats were assigned to a vehicle control group or to one of five IRDye 800BK treated groups, and were dosed by intravenous tail vein injection on Day 1 with vehicle (phosphate buffered saline) or with 12, 24, 48, 96, or 192 mg IRDye 800BK/kg body weight. Rats were necropsied on Day 15 and tissues for microscopic evaluation were collected.

IRDye 800BK was well tolerated in this study. The only effect noted that was attributed to administration of the dye was discoloration of the body and tail during the in-life portion of the study for animals receiving doses of 48 mg/kg or higher, and discoloration of the skin of the tail at necropsy for animals receiving doses of 96 mg/kg or higher. While the discoloration was considered

to be due to the presence of the dye in tissues, it was not considered an adverse effect, as it did not appear to alter any of the physiological parameters evaluated. **Based on the lack of significant lesions at any dose level, the no-observed-adverse-effect level (NOAEL) under the conditions of this study was considered to be 192 mg/kg.**

1.4.3 Single Dose Toxicity Study of IRDye 800BK Administered by Intravenous Injection to Rats

The objective of this study was to further define/determine the toxicity of IRDye 800BK when administered as a single intravenous injection to rats. Male (n=84) and female (n=84) Sprague Dawley rats were assigned to a vehicle control group or to one of three IRDye 800BK treated groups, and were dosed by intravenous tail vein injection on Day 1 with vehicle (phosphate buffered saline) or with 24, 66, or 230 mg of IRDye 800BK/kg body weight**. Because no significant adverse effects or lesions were found in the earlier Dose Range Finding Study the highest dose was increased in this study.** Animals were observed for clinical signs of toxicity and for effects on body weight, food consumption, and ophthalmology. Plasma and tissues for drug level analysis were collected after dosing on Day 1, and the plasma drug level data were subjected to toxicokinetics analysis. On Day 2 and Day 15, rats in the Core Groups were necropsied and tissues for microscopic evaluation were collected, with blood and urine for clinical pathology determinations collected prior to euthanasia.

After intravenous administration, the dye distributed rapidly to the kidney and was eliminated. These results are consistent with the plasma concentration data showing very low concentrations of dye at the 1-hour time point. The concentrations in those tissues where dye was measurable were very low and almost at the lower limit of quantitation.

Elevations in total bilirubin, alanine transaminase (ALT), and aspartate transaminase (AST) were observed for animals in the highest dose group on Day 2, however, these changes were no longer evident on Day 15. Clinical and macroscopic observations consisted of widespread blue discoloration that was considered to be due to the color of the test article, which decreased over time. Microscopic lesions were limited to minimal/mild inflammation at the injection site on the day after dosing.

Administration of IRDye 800BK had no effect on survival, body weights, food consumption, or absolute or relative organ weights of rats at any dose level. The only clinical observation recorded in the study was blue discoloration of various parts of the body. While discoloration of the urine precluded evaluation of many of the urinalysis parameters on Day 2, evaluations on Day 15 were not affected. IRDye 800BK had no effect on urinalysis parameters that could be evaluated. A follow-up Pharmacokinetic (PK) Urinalysis study addressed urinalysis parameters at an earlier time point (Day 4).

Concentrations of the dye in tissues at one (1) hour after dose administration were below the lower limit of quantitation of the assay for all samples, except the kidney of one male and three females and the lymph node of one male and in the highest dose group. The concentrations in those tissues

where dye was measurable were very low, almost at the lower limit of quantitation. These data suggest that after intravenous administration the dye distributed rapidly to the kidney and was eliminated, and are consistent with the plasma concentration data showing very low concentrations of dye at the 1-hour time point.

No sex-related differences in the toxicokinetics of IRDye 800BK were apparent among rats in the individual dose groups.

In summary, intravenous administration of IRDye 800BK was well tolerated, with no effect on survival, body weight, food consumption, or absolute or relative organ weight. Elevations in total bilirubin, ALT, and AST were observed for animals in the highest dose group on Day 2, however, these changes were no longer evident on Day 15. Clinical and macroscopic observations consisted of widespread blue discoloration that was considered to be due to the color of the test article, and that decreased over time. Microscopic lesions were limited to minimal/mild inflammation at the injection site on the day after dosing. While the discoloration, inflammation, and clinical pathology changes were considered to be due to test article administration, they were transient and were not severe enough to be considered adverse. **Based on the lack of significant lesions at any dose level, the NOAEL for IRDye 800BK under the conditions of this study was considered to be 230 mg/kg. This corresponds to an equivalent human dose of 37.1 mg/kg.**

1.4.4 Pharmacokinetic and Urinalysis Study in Rats Intravenously Administered IRDye 800BK

The objectives of this study were to determine the pharmacokinetics of intravenously administered IRDye 800BK in male Sprague Dawley rats (n=30) and to determine the effect of the dye on urine parameters. During this study, the pharmacokinetics of IRDye 800BK were investigated in rats given an intravenous (IV) dose of 24, 66, or 230 mg/kg. The results of the study indicated that the concentrations of IRDye 800BK in plasma at 0 minutes (C_0) after dosing increased with increasing dose and the increases generally were proportional to the increases in dose level. **The total body clearance and volume of distribution at steady state of IRDye 800BK for animals given 230 mg/kg were suggestive of limited hepatic or renal metabolism of IRDye 800BK and limited distribution of the dye beyond the vascular space, respectively.** It was observed that AUC_{last} values increased with increasing dose level, however, the increases in AUC_{last} values were greater than the increases in dose level. In addition, the half-life of IRDye 800BK appeared to increase with increasing dose level. **These results suggest that IRDye 800BK exhibited non-linear kinetics at the doses administered.**

The half-life of IRDye 800BK in plasma appeared to increase with increasing dose level and was 82.2 minutes for rats given 66 mg/kg and 138 minutes for rats given 230 mg/kg. These results suggest that IRDye 800BK exhibited non-linear kinetics at the doses administered, however, a terminal phase of elimination was not well characterized for animals in the 24 or 66 mg/kg dose groups, which impacted the estimation of area under the plasma concentration time curve (AUC)

values, terminal elimination half-life, and other kinetic parameters for animals in these two dose groups.

Urinalysis included the following evaluations: gross analysis (color, clarity, and specific gravity), reagent strip analysis (pH, bilirubin, ketones, protein, glucose, blood, and urobilinogen), and microscopic analysis of the urine sediment (bacteria, epithelial cells, leukocytes, erythrocytes, casts, and crystals). Urinalysis results from male Sprague Dawley rats given 0, 24, 66, or 230 mg/kg IRDye 800BK administered as a single intravenous injection were assessed on Day 4 to identify potential adverse effects. Other than a change in color, there were no notable differences in the urinalysis results on Day 4 in rats that were given 24, 66, or 230 mg/kg IRDye 800BK as compared to rats that were given the vehicle.

1.4.5 IRDye 800BK *In-Vitro* Micronucleus Assay In TK6 Cells

IRDye 800BK was evaluated for the potential to induce micronuclei in TK6 cells during short (4-hour) and long (27-hour) incubations with or without an exogenous metabolic activation system.

TK6 cultures were treated with the test article, positive control or vehicle control in the presence and absence of an Aroclor™ 1254-induced rat liver S9 microsomal fraction. IRDye 800BK concentrations tested in the range-finding assay ranged from 3.91 to 2000 µg/mL, up to the highest concentration recommended by the Organization for Economic Cooperation and Development (OECD) Guidelines. Precipitates were not observed in any treatment at the end of test article treatment. Based on the results of the range-finding assay, concentrations used during the micronucleus assay ranged from 62.5 to 2000 µg/mL. Since cytotoxicity and precipitates were not observed in any treatment level of the micronucleus assay, the highest concentrations (500, 1000, and 2000 µg/mL) were selected for the evaluation of micronuclei. These cultures, along with the vehicle and one concentration of positive control for each treatment condition, were analyzed for the presence of micronuclei. Micronuclei were evaluated in 2000 cells per concentration.

No statistically significant increases in the percent of micronucleated cells were noted between test-article treated cultures and the concurrent vehicle control under any assay condition. The data from the vehicle and positive controls demonstrated the validity and sensitivity of this test system**. IRDye 800BK was considered negative for inducing micronuclei in TK6 cells in short and/or long treatments with and without metabolic activation under the conditions of this test system.**

1.4.6 *Salmonella- E. Coli* / Mammalian Microsome Reverse Mutation Assay with IRDye 800BK (Ames Test)

IRDye 800BK was evaluated for mutagenic activity in the *in vitro Salmonella-E.coli*/ mammalian microsome reverse mutation assay. Four tester strains of *Salmonella typhimurium* (TA1537, TA98, TA100, and TA1535) and one *Escherichia coli* strain (WP2 *uvrA*) were used for mutagenicity testing. IRDye 800BK was prepared as a stock formulation in phosphate buffered saline (PBS) at concentrations of 50 mg/mL for each assay.

Mutagenicity testing was performed in triplicate at each concentration with and without an Aroclor™ 1254-induced rat liver S9 metabolic activation system. In the range-finding assay, IRDye 800BK was tested in single plates at 1, 5, 10, 50, 100, 500, 1000, and 5000 µg/plate with strains TA100 and WP2 *uvrA* using the plate incorporation method. Precipitates and cytotoxicity were not observed in either strain with or without metabolic activation. In the mutagenicity assay, IRDye 800BK was tested at 100, 250, 500, 1000, 2500 and 5000 µg/plate using the preincubation method. Precipitates were not observed in any strain with or without metabolic activation. Cytotoxicity (i.e., reduction in the background lawn and/or mean number of revertant colonies) was observed in strain TA1537 at ≥ 2500 µg/plate without metabolic activation and at 5000 µg/plate with metabolic activation.

In the mutagenicity assay, criteria for a negative response were met for all tester strains with and without metabolic activation. The mean number of revertant colonies was comparable to historical control ranges at all concentrations for all tester strains with and without metabolic activation. The data from the vehicle and positive controls demonstrated the validity and sensitivity of this test system for detecting chemical mutagens with and without metabolic activation. **These data support the conclusion that IRDye 800BK is negative for mutagenic activity in the *Salmonella* strains TA1537, TA98, TA100, and TA1535 and in the *E. coli* strain WP2 *uvrA*, with and without metabolic activation, under the conditions of this assay.**

1.5. Overview of Clinical Experience

This is the first human study in the development of IRDye 800BK as an imaging agent. Structurally, IRDye 800BK is closely related to the carboxylate form of IRDye® 800CW, whose cetuximab and panitumumab conjugates are currently undergoing FDA-approved clinical trials, [IRDye® 800CW-labeled cetuximab (IND# 115706) and IRDye® 800CW-labeled panitumumab (IND# 119474)].

1.6. Risks / Benefits Assessment

IRDye 800BK belongs to the heptamethine indocyanine class of dyes that are characterized by a low inherent toxicity. Given the innocuous chemistry of indocyanines in general (Tanaka et al., 2008), IRDye 800BK is not expected to exert significant adverse pharmacological effects on trial subjects. It is expected that the use of IRDye 800BK should enable the recognition of the pelvic ureter, increase the efficiency of pelvic/abdominal surgeries, and lead to a reduction in operative time as well as the associated operating room costs. Use of this dye should also lead to a reduction in the incidence of urinary tract complications and the associated morbidity. Resource savings can be considerable given the costs associated with repeat surgeries, additional hospitalizations, and medicolegal implications and costs.

1.7. TREATMENT RATIONALE FOR THIS STUDY

Clear identification of ureters is often very difficult to do but remains essential in order to avoid inadvertent ureteral injury. Currently available technologies include preoperative ureteral radiographic imaging and the use of illuminating stents, and both have notable shortcomings. Radiographic imaging is not considered particularly helpful during surgery itself, whereas the placement of illuminating stents can be unnecessarily cumbersome to use for low risk surgery. The development of a low toxicity dye which enables good visibility of the urinary tract anatomy could offer better surgical outcomes for various pelvic and abdominal procedures.

1.8. RATIONALE FOR IP DOSE SELECTION

Dose selection for this study was based on an initial pre-clinical study using a porcine model at four different dosing cohorts of IRDye 800BK: 0.03 mg/kg, 0.06 mg/kg, 0.09 mg/kg, and 0.12 mg/kg. The porcine pelvic ureter was identified in all animals (12 total) with a direct relationship between the actual dose and time to visualize the ureter, visualization of the entire ureter, and the intensity of the signal (qualitative assessment). Specifically, as the dose increased, the ureter was more quickly visualized and the entire length of the pelvic ureter was seen with persistence of the signal intensity out to 60 minutes. There were no observed physiologic events (i.e., tachycardia, bradycardia, hypotension) as the dose increased. Of note, as the dose increased, there was increasing background interference with signal specifically detected from the porcine uterine horns. The PINPOINT Endoscopic Fluorescence Imaging System™ laparoscopic and near-infrared fluorescence imaging system was utilized for this study. Based on this study, 0.06 mg/kg was determined to be the initial dose used for starting the dose range-finding study. Using the FDA Guidance "M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals," and the approach outlined therein, it has been determined that the maximum human dose could be as high as 3.7 mg/kg.

2. STUDY OBJECTIVES

The following outlines the objectives of the study and how safety will be measured. Efficacy measurements are also delineated.

2.1. OBJECTIVES

The objectives of this study are:

- To determine the safety of IRDye 800BK Injection in the detection of pelvic urologic anatomy, particularly the ureter, via NIRF imaging in female subjects undergoing minimally invasive surgery.
- To determine the efficacy of IRDye 800BK Injection for the detection of pelvic urologic anatomy, particularly the ureter, via NIRF imaging in female subjects undergoing minimally invasive surgery

Part A only:

- To assess the dose response and determine the timing interval for the detection of pelvic urologic anatomy, particularly the ureter, via NIRF imaging in female subjects undergoing minimally invasive surgery

Part B only:

- To verify that the image score of the near optimal dose determined in Part A is in agreement with a selection of commercially available endoscopic imaging systems. The systems selected are the PINPOINT Endoscopic Fluorescence Imaging System (Novadaq) and Stryker Infrared Illuminating System (IRIS) [AIM light source].

2.2. STUDY OUTCOMES (ENDPOINTS)

2.2.1 Safety Outcome Measures

The safety outcome measurements for the study will be primarily assessed by:

- Evaluation of injection site reactions
- Incidence of Treatment-Emergent Serious Adverse Events (TESAE)
- Incidence of Treatment-Emergent Adverse Events (TEAE)
- Incidence of UADEs related to imaging devices
- Incidence of withdrawals from the study due to TEAEs and/or UADEs
- Changes and shifts in laboratory measurements over time

2.2.2 Efficacy Outcome Measures

Part A:

The efficacy outcomes for the study will be primarily assessed by:

- Dose response based on the composite assessment of the anatomy and laterality for detection of pelvic ureter in women undergoing minimally invasive surgery. This outcome is measured by the composite scores from the following ureteral imaging scales; 0 being the worst and 4 being the best:
  - i) Anatomy: Entire ureter length from pelvic brim down (2); Partial length (1); or No signal visualized (0).
  - ii) Laterality: Bilateral (2); Right ureter only or Left ureter only (1); or None (0).
- Time to ureter visualization post-infusion from 10 minutes through 90 minutes.
- Anatomical detection of pelvic ureter using ureteral imaging scales (i.e., the entire ureter length from pelvic brim down, partial length, or no signal visualized).
- Lateral detection of pelvic ureter using ureteral imaging scales (i.e., bilateral, right ureter only or left ureter only, or none)
- Length of time the ureter is visible.

Part B:

The efficacy outcomes for Part B are exploratory and will be assessed by:

- the composite assessment of the anatomy and laterality for detection of pelvic ureter in women undergoing minimally invasive surgery, as collected on the da Vinci Firefly Imaging System and either the Novadaq PINPOINT Endoscopic Fluorescence Imaging System or Stryker Infrared Illuminating System (IRIS) [AIM light source] devices real time, within the same subject. Images are captured post-infusion at the identified near-optimal dose at 10 and 30 minutes. The image results will show the degree of agreement between imaging scores can be obtained across several medical imaging devices. The image results are measured using the ureteral imaging scales described for Part A.

3. STUDY DESIGN

This is a single site, Phase I/IIa, dose-escalation study evaluating the use of IRDye 800BK Injection to detect urologic structures, particularly the ureter, with NIRF imaging, in women undergoing minimally invasive pelvic surgery. The safety and efficacy of IRDye 800BK Injection will be assessed after each dose cohort. There will be two Parts to this study. The objective of Part A is to determine safety of the dye and the near optimal dose based on a dose escalation/de-escalation study using the da Vinci Firefly imaging device. The objective of Part B is to show that similar imaging scores can be obtained with a selection of commercially-available medical imaging devices. There will be at least eight (8) subjects per cohort for Part A. Part B will have at least 8 subjects assessed with the da Vinci Firefly Imaging System and the Novadaq PINPOINT Endoscopic Fluorescence Imaging System device, and at least 8 subjects assessed with the da Vinci Firefly Imaging System and the Stryker Infrared Illuminating System (IRIS) [AIM light source].

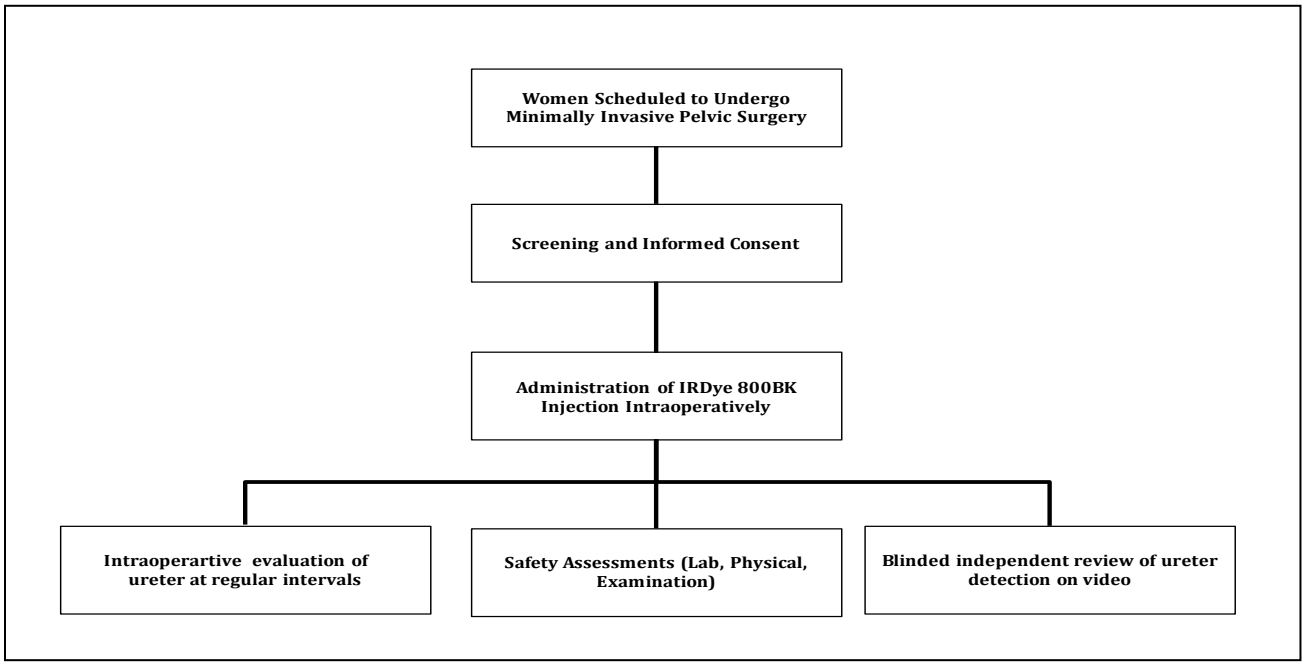
PART A:

Each cohort of at least 8 subjects will be given a single dose of IRDye 800BK Injection, starting at 0.06 mg IRDye/kg body weight. In the absence of any safety concerns, and based upon the imaging scores, the dose of IRDye 800BK Injection may increase or decrease for each successive cohort. The near optimal dose will be selected based on the following criteria:

- the highest proportion of subjects that achieve a maximum Ureteral Imaging Score of "4"
- the shortest average time to visualization, and
- the longest average duration of time that the Ureteral Imaging Score remains at least "3"

For each cohort in Part A, an Independent Data Safety Monitoring Committee (DSMC) will review the safety data and imaging scores collected after all subjects within the cohort completed treatment. In the absence of any safety concerns, and based upon the imaging scores, the Independent DSMC will authorize escalation/de-escalation to the next dose. The study flow diagram is presented in Figure 3 1.

Figure 3-1: Study Flow Diagram Part A



Part B:

Two cohorts of at least 8 subjects each will be given the near optimal dose obtained from Part A. Imaging data will be collected at 10 and 30 minutes (±5 minutes) post-infusion and scored for visualization of the ureter using the visualization scale found in 4.2.3, using either the da Vinci Firefly Imaging System and the Novadaq PINPOINT Endoscopic Fluorescence Imaging System (at least 8 subjects) or the da Vinci Firefly Imaging System and the Stryker Infrared Illuminating System (at least 8 subjects). Unlike Part A, the imaging scores will be collected at 10 and 30 minutes only for Part B. The composite ureteral imaging assessments will be compared between devices at these 2 time points for each cohort. The results are being collected for information only. The degree of concordance at 10 minutes and 30 minutes will be calculated in a paired manner within each subject.

Because the near-optimal dose has already been safely established, DSMC review is not needed for Part B and the two cohorts can be run concurrently (i.e. the cohort using the Novadaq PINPOINT Endoscopic Fluorescence Imaging System as the second device does not have to be completed before the cohort using the Stryker Infrared Illuminating System (IRIS) begins).

3.1. STUDY CENTER

This is a single site study conducted in the United States at the University of Alabama at Birmingham.

3.2. STUDY POPULATION

This study will recruit adult (>18 years of age) female patients undergoing standard of care minimally invasive pelvic surgery (traditional laparoscopy and robotic surgery), and who are expected to be admitted to the hospital following surgery for at least 24 hours.

Subject enrollment will be staggered by dose group to facilitate adequate safety and efficacy review by the DSMC. Each dose group will have data from eight (8) evaluable subjects.

3.3. ELIGIBILITY CRITERIA

3.3.1 Inclusion Criteria

Potential subjects are required to meet all of the following criteria for enrollment into the study:

1. Provide written informed consent prior to the initiation of study procedures.
2. Are > 18 years of age.
3. Women consented to undergo standard of care minimally invasive pelvic surgery (traditional laparoscopy and robotic surgery).
4. Women who are expected to be admitted to the hospital following surgery for at least 24 hours.

3.3.2 Exclusion Criteria

Potential subjects meeting any of the following criteria will be excluded from enrollment:

1. Are unwilling or unable to provide informed consent.
2. Are unwilling or unable to comply with the requirements of the protocol.
3. History of prior urologic surgery.
4. History of prior pelvic surgery.
5. History of known retroperitoneal fibrosis.
6. Have any of the following screening laboratory values:
    a. Hemoglobin ≤ 8.0 g/dL;
    b. Absolute neutrophil count (ANC) ≤ 1500/µL;
    c. Platelet count ≤ 100,000/µL;
    d. Serum creatinine ≥ 1.5 x the institutional upper limit of normal (IULN);
    e. Serum bilirubin ≥ 1.5 x IULN;
    f. Aspartate transaminase (AST) (serum glutamic oxaloacetic transaminase, SGOT) ≥ 2 x IULN;
    g. Alanine transaminase (ALT) (serum glutamate pyruvate transaminase, SGPT) ≥ 2 x IULN.
7. Females who are pregnant, lactating, or breastfeeding.
8. Patients having undergone a sentinel lymph node biopsy.

9. Any other condition that, in the Investigator's judgment, would potentially compromise study compliance or the ability to evaluate safety or efficacy.

3.4. STUDY RISKS

3.4.1 Non-Significant Risk Devices

The current intended use statements of the imaging medical devices specified in this protocol do not cover the structural delineation of the ureters. However, there are no modifications to either the mechanical specifications or the user protocols required for the imaging and structural delineation of the ureters. A full description of the comparison of FDA cleared and clinically relevant NIR fluorescent imagers and the justification for determination of the imaging devices as "Non-Significant Risk" devices can be found in the "Non-Significant Risk Justification" document in Appendix 2, Section 17.2.

3.4.2 Risk Assessment

The risk determination is based on the proposed use of the imaging device in an investigation in conjunction with the IRDye 800BK, and not on the device alone. The subjects will not need to undergo an additional procedure as part of the investigational study.

Specifically, NIR wavelengths are low energy and do not pose a risk to the end user, therefore the use of NIR dyes in a surgical setting does not require the use of any special safety equipment for use or viewing in the surgical field.

The imaging described in Part B of the study requires an additional imaging device (i.e. endoscope) to be used to obtain a ureteral image. All of the surgeries described in Part A and Part B follow the standard of care with the da Vinci Firefly device. Four to five ports are used for laparoscopic surgeries. The additional imaging device will be placed in one of the standard accessory ports. No additional incisions will be required to use these other imaging devices. The image collection and reporting should take two minutes at the most and as such, will not prolong the surgery significantly.

4. STUDY SCHEDULE

This study is divided into three periods: Screening, Treatment, and Post-Procedure.

Procedures to be performed during each of these study periods are described in the subsequent section and provided as a Schedule of Events in Table 4-1.

Table 4-1: Schedule of Events

Procedure/Assessments	Screening Visit Visit 1	Qualification	Pre-Treatment Visit 2	Surgery	12 H Post-Op Visit 3	24 H Post-Op Visit 4	Follow up Visit 5
Visit	**SV**	**Qualification Notification**	**Pre-Op**	**Surgical**	**Post-Op**	**Post-Op**	**Follow-up Visit or Phone Check**
Window Period	30 to -1 days prior to treatment	Within 24 hours of surgery			Within 12 hours after surgery	Within 24 hours after surgery	Day 28 ± 5 days
Informed Consent[1]	X						
Eligibility Evaluation and subject notification[2]		X					
Subject Demographics	X						
Medical and Surgical History[3]	X						
Full Physical Examination	X					X	
Vital Signs[4]	X		X	X	X	X	
Body Weight & Height BMI	X		X[5]				
ECG	X				X	X	
Complete Blood Count (CBC)[6]	X				X	X	
Biochemistry[7]	X				X	X	
Coagulation Indices[8]	X				X	X	
Urine Pregnancy Test	X		X				
Routine Urinalysis	X				X	X	
IRDye 800BK Injection Administration				X			
Image reading[9]				X			
Phone Check[10]							X
Adverse Events			X	X	X	X	X

Procedure/Assessments	Screening Visit Visit 1	Qualification	Pre-Treatment Visit 2	Surgery	12 H Post-Op Visit 3	24 H Post-Op Visit 4	Follow up Visit 5
Visit	**SV**	**Qualification Notification**	**Pre-Op**	**Surgical**	**Post-Op**	**Post-Op**	**Follow-up Visit or Phone Check**
Window Period	30 to -1 days prior to treatment	Within 24 hours of surgery			Within 12 hours after surgery	Within 24 hours after surgery	Day 28 ± 5 days
Concomitant Medications	**X**		**X**	**X**	**X**	**X**	
Treatment Number Assignment			**X**				

[1] Informed consent must be obtained prior to patient participation in any protocol-related activities that are not part of routine care.

[2] Evaluation of patient eligibility will be performed by Investigator. A review of all laboratory and examination results will be performed. The subject will be notified of their qualification status.

[3] Medical history, past surgeries, disease history, history of substance abuse, social history and current therapies (medications and non-medications).

[4] Blood pressure, heart rate, temperature.

[5] Weight only.

[6] Hemoglobin, hematocrit (Hct), red blood cells (RBC), white blood cells (WBC) with total and differential count, absolute neutrophil count (ANC), and platelets.

[7] Hepatic function indicators: total and direct bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, lactate dehydrogenase (LDH)

Renal function indicators: BUN, creatinine.

[8] PT, PTT, INR.

[9] Part A scoring will be done at post-infusion time: 10 minutes, 20 minutes, 30 minutes, 45 minutes, 60 minutes, 75 minutes and 90 minutes (all ±5 minutes). Vital signs and an infusion site check will also be performed. Part B scoring will be done at post-infusion time points: 10 and 30 minutes (±5 minutes). Vital signs and an infusion site check will also be performed.

[10] If the subject cannot return for a day 28 visit to the clinic.

4.1. SCREENING PERIOD

The screening phase is designed to determine whether subjects are eligible to proceed to the Treatment Phase. The subject will sign and date the informed consent form (ICF) and the Health Insurance Portability Accountability Act (HIPAA) authorization according to the institution's policy and practices prior to any study related procedures being performed. A unique identification number (screening number) will be assigned to each subject who has provided written informed consent. The subject screening number will be a three-digit numeric assigned in successive order of entering the study, beginning with 001.

The study site will be instructed to maintain the study-specific pre-screening, screening, and enrollment logs. If a subject initially fails to meet inclusion/exclusion criteria, she cannot be reconsidered for enrollment unless her scheduled surgery was also canceled. If that is the case, she may rescreen only one time.

4.1.1 Screening Visit (SV)

After the Informed Consent Form (ICF) has been signed, screening procedures and information will be obtained to confirm subject eligibility. This visit may be performed up to 30 days prior to the scheduled treatment visit but not less than 24 hours prior to surgery. The procedures to be administered during this visit include:

- A detailed medical and surgical history;
- Demographic information;
- Current medications and medications taken within 30 days of anticipated treatment date;
- Full physical examination;
- Electrocardiogram (ECG);
- Body weight and height measurements and calculated Basal Metabolic Index (BMI);
- Vital signs including temperature;
- Collection of blood specimens for:
    - Routine complete blood count (CBC);
    - Biochemistry;
    - Coagulation Indices [Prothrombin time (PT) and International Normalized Ration (INR)];
    - Collection of a urine specimen for routine urinalysis; and
    - Urine pregnancy test.

All screening information will be fully documented in the subject's medical records (i.e., source documents).

For consented subjects who do not meet eligibility criteria, a Screen Failure Case Report Form (CRF) will be completed. The Screen Failure CRF will contain the following details: the subject identification number, the date of ICF signature, demographic information (see section 7.3), and the reason for screen failure. No additional information will be required for subjects who fail screening.

For consented subjects who meet eligibility criteria, all required screening information will be entered in the electronic CRF (eCRF). The subjects in Part B of the study will be assigned the imaging devices that will be used for visualization at this time. The first eight subjects enrolled will be assigned to the Novadaq PINPOINT Endoscopic Fluorescence Imaging System and the next eight subjects will be assigned to the Stryker Infrared Illuminating System.

Within 24 hours prior to the surgical procedure and administration of the imaging product, the investigator will review all the laboratory and examination results. If the subject qualifies for the study, a phone call will be made and documented that the subject is aware of her qualification and still wishes to continue with the study.

4.2. TREATMENT PERIOD

The Treatment Period begins with an evaluation of the results of laboratory samples collected at the Screening Visit. Subjects who meet all eligibility criteria and none of the exclusion criteria, as per data gathered from Screening Visit, are qualified to receive imaging with IRDye 800BK Injection. All subjects who fail to meet eligibility criteria will be considered screen failures and exit the study without further evaluation.

4.2.1 Pre-Operative Procedures (Visit 2)

The research pharmacy will be notified in advance of the scheduled surgery. IRDye 800BK Injection will be reconstituted in the research pharmacy and delivered to the operating room after the subject is brought to the operating room. The dosing syringe specific to the subject will be appropriately labeled by the research pharmacy staff, including the treatment number assigned sequentially. The dose will be confirmed by anesthesia and the surgeons and/or assistants via a verbal 'timeout' format per the institution's process and procedure.

The procedures to be administered prior to surgery include:

- Current medications and medications taken since the screening visit;
- Vital signs including temperature (ECG in Part A only);
- Urine pregnancy test for women of reproductive age;
- Assessment of adverse events since the last visit;
- Assessment of changes in concomitant medications since the last visit;
- Weight only; and
- Treatment number assignment.

All information will be fully documented in the subject's medical records (i.e., source documents).

4.2.2 Intraoperative Procedures

After reconstitution with half-normal saline, IRDye 800BK Injection will be administered via intravenous push by trained study staff followed by a saline flush of the IV catheter (at least 10 mL). The entire volume in the syringe will be given. This will be administered after the endoscope has been successfully inserted into the abdominal cavity.

Part A Near-Optimal Dose Determination: Using NIRF technology (Firefly™ from Intuitive Surgical), visualization of the pelvic ureter will be performed every ten minutes for the first thirty minutes, then every 15 minutes up through 90 minutes. If visualization continues after 90 minutes, sites are requested to continue until visualization degrades. Table 4-2 outlines the specific time points.

Part B Additional Device Images: Visualization of the ureter for Part B will be recorded at 10 (±5 minutes) and 30 minutes (±5 minutes) post-infusion of IRDye 800BK. Images will not be recorded every 10 minutes as in Part A. The ureter will be imaged with the da Vinci Firefly Imaging System and either the Novadaq PINPOINT Endoscopic Fluorescence Imaging System or Stryker Infrared Illuminating System (IRIS) [AIM light source]. The surgery will be conducted using the da Vinci Firefly Fluorescence Imaging System. At the time points indicated above, either the Novadaq PINPOINT Endoscopic Fluorescence Imaging System or Stryker Infrared Illuminating System (IRIS) [AIM light source] will be used to collect a ureteral image. The images will be scored according to the scale outlined in section 4.2.3. At the same time points, the image score from the da Vinci Firefly Imaging System will be recorded using the same scale. The image scores taken with different imaging devices at the same time points will be compared to each other for information only.

These surgeries follow the standard of care with the da Vinci Firefly device. Four to five accessory ports are used for these surgeries. One of these ports is repurposed at the two specified time points. At the specified time points, the additional imaging device (i.e., endoscope) will be placed in the repurposed standard accessory port. No additional incisions/ports will be required to use these other imaging devices. The standard of care for these patients will not be altered based on the images obtained under this protocol. This additional imaging should take two minutes at the most and as such, will not prolong the surgery significantly.

Eight patients will be imaged with the da Vinci Firefly Imaging System and the Novadaq PINPOINT Endoscopic Fluorescence Imaging System and eight patients with the da Vinci Firefly Imaging System and the Stryker Infrared Illuminating System (IRIS). An image will be captured at 10 and 30 minutes from each imaging system per patient and scored accordingly using white light and NIRF.

Table 4-2: Intraoperative Vital Signs, IV Site Check and Visualization Time points for Part A

Timepoint	Schedule Marker
T-1	The laparoscope has been successfully inserted into the abdominal cavity. Baseline images are captured.

T_0	IRDye™ 800BK Injection is administered. Do not count flush time
10 minutes ± 5 min	Post Administration image visualization, vital signs and IV site reaction
20 minutes ± 5 min	Post Administration image visualization, vital signs and IV site reaction
30 minutes ± 5 min	Post Administration image visualization, vital signs and IV site reaction
45 minutes ± 5 min	Post Administration image visualization, vital signs and IV site reaction
60 minutes ± 5 min	Post Administration image visualization, vital signs and IV site reaction
75 minutes ± 5 min	Post Administration image visualization, vital signs and IV site reaction
90 minutes ± 5 min	Post Administration image visualization, vital signs and IV site reaction

Table 4-3: Intraoperative Vital Signs, IV Site Check and Visualization Time points for Part B

Timepoint	**Schedule Marker**
T-1	The laparoscope has been successfully inserted into the abdominal cavity. Baseline images are captured.
T_0	IRDye™ 800BK Injection is administered. Do not count flush time
10 minutes ± 5 min	Post Administration image visualization with the PINPOINT Endoscopic Fluorescence Imaging System and the da Vinci Firefly Imaging System OR Post Administration image visualization with the Stryker Infrared Illuminating System (IRIS) [AIM light source] and the da Vinci Firefly Imaging System Vital signs and IV site reaction for all subjects
30 minutes ± 5 min	Post Administration image visualization with the PINPOINT Endoscopic Fluorescence Imaging System and the da Vinci Firefly Imaging System

	OR Post Administration image visualization with the Stryker Infrared Illuminating System (IRIS) [AIM light source] and the da Vinci Firefly Imaging System Vital signs and IV site reaction for all subjects

Findings at each time point will be documented in the appropriate eCRF using the ureter imaging scale described in Section 4.2.3.

For Part A, vital signs (data to be procured from anesthesia) and an assessment of the IV infusion site (for redness, swelling, and/or infiltration) of the imaging dye will be obtained every 10 minutes for the first 30 minutes and every 15 minutes thereafter. Vital signs and the IV site assessment will be documented in the appropriate eCRF.

For all subjects, the entire procedure will be video recorded for independent review and scoring of NIRF pelvic ureteral imaging by at least one blinded surgeon. The ureteral imaging score will be collected on a scoresheet. This information is being collected for information only.

For Part B, an image will be captured at each time point (10 minutes and 30 minutes, ± 5 minutes) from each imaging system per patient and scored using the ureter imaging scale described in Section 4.2.3.

4.2.3 Ureteral Imaging Scale (used for both Part A and Part B)

The following ureteral imaging scale will be used to standardize reporting of NIRF *in vivo* imaging of the pelvic ureter:

1) Anatomy:

Score of 2: Visualization of the entire ureter length from pelvic brim down;
Score of 1: Visualization of partial length of the ureter; or
Score of 0: No signal visualized.

2) Laterality:

Score of 2: Bilateral visualization of the ureters;
Score of 1: Visualization of only the right ureter or only the left ureter; or
Score of 0: Neither ureter is visualized.

Thus, as an example, a patient with visualization of partial length of the right side only would have a score of 2.

4.2.4 Post-Operative – 12 hours (Visit 3) -

Within 12 hours of surgery, the following procedures will take place:

- CBC;
- Biochemistry;
- Coagulation indices;
- Urinalysis;
- Vital Signs;
- ECG;
- Concomitant medications;
- Adverse events (clinician to classify between surgical versus non-surgically related adverse events).

4.2.5 Post-Operative – 24 hours (Visit 4)

Within 24 hours of surgery, the following procedures will take place:

- CBC;
- Biochemistry;
- Coagulation indices;
- Urinalysis;
- Vital Signs;
- Full Physical Exam;
- ECG;
- Concomitant medications;
- Adverse events (clinician to classify surgical versus non-surgically-related adverse events).

4.3. POST-OPERATIVE DAY 28 (VISIT 5)

On day 28 ± 5 days post-surgery, the subject may return for a post-operative exam. At that time, the investigator will determine if any adverse events not related to the surgery are present. If the subject does not return for a post-operative visit within the prescribed timeframe, the study site will call the subject to ascertain if any adverse events are present. The investigator will follow any possible, probable or definitely related to study product adverse events until resolution.

4.4. UNSCHEDULED VISITS

In the event that the subject presents to the clinic at a time other than a regularly scheduled study visit, the visit will be regarded as an unscheduled visit. Assessments at unscheduled visits are at

the discretion of the Investigator. All pertinent findings, including adverse events or changes in medications will be noted in the eCRF.

4.5. INDEPENDENT VIDEO REVIEW

Each surgery will be video recorded by the Investigator or delegate for independent review by at least one blinded surgeon not associated with this clinical trial. Using the ureteral imaging scale described above (Section 4.2.3), all time points will be scored by the blinded surgeon during the review of the surgical video but are not entered into the study database. Detailed instruction on the submission and rating for independent review will be outlined in the Study Operations Manual.

5. SUBJECT COMPLETION, WITHDRAWAL AND CRITERIA FOR STOPPING THE STUDY

5.1. SUBJECT COMPLETION

A subject who completes all study periods, receives the study product, and completes the follow-up visit and/or phone call will be considered as having completed the study.

5.2. SUBJECT WITHDRAWAL

At any point during the study all subjects have the right to withdraw without prejudice to future care. Documentation of whether or not each subject completed the clinical study will be recorded. If study treatment was discontinued for any subject, the reason(s) will be documented. The subject should have a final visit inclusive of a full physical exam, vital signs, ECG, CBC, biochemistry, coagulation labs, urinalysis, and assessment of adverse events and changes to medications.

5.3. WITHDRAWAL CRITERIA

The Investigator can discontinue a subject at any time, if in his/her clinical judgment he/she considers it to be medically necessary. Investigators considering discontinuing study treatment should contact the medical monitor prior to such discontinuation. Subjects who have study treatment discontinued will continue to be followed, per protocol, whenever possible. Subjects who have study treatment discontinued due to a serious adverse event (SAE) will be followed until resolution or stabilization of the event.

All subjects have the right to withdraw at any point during treatment without prejudice to future care. It will be documented whether or not each subject completed the clinical study. If study treatment or observations were discontinued for any subject, the reason(s) will be recorded.

Withdrawal rules have been defined as followed:

- Occurrence of an anaphylactic or other significant allergic reaction to IRDye 800BK Injection.
- Ongoing clinical adverse event related to the IRDye 800BK Injection.
- Occurrence of a SAE related to IRDye 800BK Injection.
- Occurrence of an UADE related to the imaging device.
- A subject is significantly non-compliant with the requirements of the protocol.
- The investigator determines that it is in the best interest of the subject.
- Subject chooses to withdraw or is withdrawn due to an adverse event.
- Discontinuation of the study by the Sponsor.

- Subject withdrew consent.

5.4. DATA COLLECTED FROM WITHDRAWN SUBJECTS

Every attempt should be made to collect follow-up information. The reason for withdrawal from the study will be recorded in the source documents and in the appropriate page of the eCRF.

Before a subject is identified as lost-to-follow up, the site should make all reasonable efforts to contact the subject. These attempts must be documented and should include, at a minimum, one phone call and one certified letter.

In the event that a subject is withdrawn from the study at any time due to an adverse event or SAE, the procedures stated in Section 5.2 (Subject Withdrawal) must be followed.

Screen Failures

A Screen Failure will be classified as a subject who signed a consent form but did not meet the inclusion/exclusion criteria. Subject number, ICF signature date, demographics (as mentioned in Section 7.3), and a reason for screen failure will be recorded.

In the event that a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the subject may be re-consented and assigned a new screening number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened only one (1) time and may be enrolled if they are found to meet all inclusion and no exclusion criteria at the subsequent screening visit.

5.5. STOPPING RULES

Safety endpoints for each dose group will be reviewed by the DSMC prior to advancing to the next dose. In the event that more than two subjects have a SAE (Grade 3 or more as defined by the toxicity grading scale) directly related to the study product and that cannot be attributed to any other cause, the study will be placed on hold until further evaluation by the DSMC.

6. STUDY TREATMENT

6.1. METHOD FOR ASSIGNING ELIGIBLE SUBJECTS TO TREATMENT

The Investigative Pharmacist will be given a list of treatment numbers by dose. Within 24 hours prior to surgery, the Pharmacist will verify with the Investigator the dose group and assign the treatment number sequentially. A written authorization to proceed to the next dose group will be given to the Investigator from the DSMC.

6.2. DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

The name of the investigational product is IRDye 800BK Injection.

IRDye 800BK is a near-infrared imaging agent that is intended to be used as a surgical aid to visualize urine in the ureters and the bladder and allow their structural delineation during pelvic or abdominal surgery.

6.2.1 Drug Substance

Proprietary Name: IRDye 800BK

Chemical Name: 3H-Indolium, 2-[2-[3-[2-[1,3-dihydro-3,3-dimethyl-5-sulfo-1-(4-sulfobutyl)-2H-indol-2-ylidene]ethylidene]-2-(4-sulfophenoxy)-1-cyclohexen-1-yl]ethenyl]-3,3-dimethyl-5-sulfo-1-(4-sulfobutyl)-, inner salt, sodium salt (1:4)

Chemical Formula: C44H48N2Na4O16S5

Molecular Weight: 1113.1

CAS No.: 262284-03-7

Appearance: Olive-green to golden crystals; aqueous solution is blue-green in color

Solubility: Soluble in water, methanol, dimethylsulfoxide (DMSO), and dimethylformamide (DMF).

Optical properties: Absorbs and emits light at near-infrared wavelengths.

6.2.2 Drug Product

IRDye 800BK Injection is a lyophilized sterile vialed product which contains 25 mg IRDye™ 800BK drug substance, 214 mg mannitol (as a bulking agent), and 9.6 mg citric acid (as a buffer) per vial prior to reconstitution. Prior to IV administration, the product is warmed up to room temperature for at least 1 hour and reconstituted with 10 mL of half normal saline (0.45% aqueous sodium chloride solution) to a final drug concentration of 2.46 mg/ml.

Prior to reconstitution, IRDye 800BK Injection is a dark green-blue lyophilized cake. After reconstitution, the product is an intense green-black solution free of particulates.

Figure 6-1 outlines the product label. Figure 6-2 outlines the syringe label.

Figure 6-1: Product Label

IRDye 800BK Injection **Protocol: LICOR-10417-01**

Lot PLI011-16

Storage: 5 ± 3°C; protect from light

Reconstituted: store 25 ± 2°C up to 24 hours; ambient light

CAUTION: New drug - limited by United States law to Investigational Use

LI-COR, Inc. 4647 Superior St, Lincoln NE USA 68504

Figure 6-2: Syringe Label

Protocol: LICOR-10417-01 Subject No: ___ ___ ___ ___

This syringe contains _____ mL **IRDye™ 800BK** (Cohort:__ mg/mL) solution for intravenous injection.

Prepared: _ _/_ _/_ _ _ _ Time: _____

USE AS PER STUDY PROTOCOL

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use

LI-COR, Lincoln, NE, USA

6.2.3 Investigational Product Storage and Handling

Prior to reconstitution, the product is to be stored at 2-8°C protected from light. After reconstitution, the product solution can be stored at room temperature and with ambient light for up to 24 hours.

6.2.4 Study Product Preparation

6.2.4.1 Reconstitution procedure for IRDye 800BK Injection solution

The following describes the general procedure to prepare IRDye 800BK Injection solution for administration to subjects. Detailed information is found in the Pharmacy Manual.

a. A 25 mg/20 mL vial of dry/lyophilized IRDye 800BK Injection will be allowed to

equilibrate to room temperature (approximately 1 hour).

b. The contents of the vial will be diluted with 10 mL of 0.45% (half-normal) saline. The final stock dye concentration will be 2.46 mg/mL.

c. The IRDye 800BK Injection solution should be maintained at room temperature. Do not store longer than 24 hours after reconstitution.

d. Calculation of dose: The total IRDye 800BK (mg) required is calculated by multiplying the subject weight (in kg) by the intended dose cohorts.

$$Total\ mg\ required = weight\ of\ subject\ (kg) * expected\ dose\ (\frac{mg}{kg})$$

The total injected dose volume (mL) of IRDye 800BK Injection solution is calculated by dividing the total mg required (calculated in step 1) by the stock dye concentration (2.46 mg/mL).

$$Dose\ Volume\ (mL) = \frac{Total\ mg\ required}{2.46\frac{mg}{mL}}$$

e. The prepared patient dose syringe will be clearly labeled with:

1. Date and Time of preparation;
2. Dose cohort;
3. Subject ID; and
4. Concentration.

6.2.4.2 Investigational Product dosage and frequency of application

Each subject will receive one injection of IRDye 800BK Injection solution immediately following confirmation that the laparoscope has been successfully inserted into the abdominal cavity. The starting product dosage (Cohort 1) will be 0.06 mg IRDye 800BK/kg body mass for each of the 8 subjects in the cohort. For subjects in Part A of the study, the dose may be increased or decreased based on the visualization scores and the decision of the DSMC. Subjects in Part B of the study will receive the near-optimal dose as determined by Part A of the study.

For each subject in Part A, a Ureteral Imaging Score will be recorded by the PI every ten minutes for the first thirty minutes, then every 15 minutes up through 90 minutes or beyond (see

Section 4.2.2, Intraoperative Procedures and 4.2.3, Ureteral Imaging Scale, for more information). Additionally, scoring at the same time points will be determined by at least one surgeon performing a blinded review of the surgery video recording. This data will be used to report the following for Cohort 1 and each subsequent cohort:

1) Initial time to visualization, defined as the first time point where the Ureteral Imaging Score is at least "2" (partial laterality and partial anatomy)
2) Maximum Ureteral Imaging Score achieved during the surgery
3) Duration that the Ureteral Imaging Score remained at least at a score of "3"

This data will be used to evaluate the need for additional cohorts in order to identify the near-optimal dose for ureteral imaging. The near-optimal dose will be the lowest dose determined to give:

1) the highest proportion of subjects that achieve a Ureteral Imaging Score of “4”
2) the shortest average time to visualization, and
3) the longest average duration of time that the Ureteral Imaging Score remains at least "3"

After each cohort, a Data Safety Monitoring Committee will review safety data to determine that the trial can continue and no safety issues have arisen. Barring any safety concerns, the Committee will review the proportion of subjects that were given a Ureteral Imaging Score of “4," the mean and median times to visualization, the mean and median times that a score of "4" was reached (if at all), and the mean and median times that the Ureteral Imaging Score remained at least a "3." Based on this data, a decision will be made to

1) Stop the study because the near optimal dose has been determined
2) Continue the study by increasing the dose because improved efficacy is expected, or
3) Continue the study by decreasing the dose to determine the lowest fully effective dose.

LI-COR will determine the next dosing level based on recommendations from the PI and the DSMC. In no case will the dose exceed 3.7 mg/kg.

Each subject in Part B will be dosed with the near-optimal dose determined in Part A of the study. Images will be taken at 10 and 30 minutes after administration. These images will be scored via the Ureteral Imaging Scale found in section 4.2.3. Because the DSMC has already determined that the administered dose is safe, no DSMC review is required after Part B.

6.3. INVESTIGATIONAL PRODUCT ORDERING

The investigational site will order product in accordance with directions in the Operational Manual.

6.4. INVESTIGATIONAL PRODUCT PACKAGING

IRDye 800BK Injection is packaged in clear sealed glass vials, protected from light.

Study treatment will be labeled, according to the regulatory guidelines, as an investigational product to ensure that the IP will not be used outside of the clinical investigation. The Sponsor name, protocol number, and any additional relevant information will appear on the pack label.

6.5. INVESTIGATIONAL PRODUCT DISPOSITION

The IP will be delivered to the site research pharmacist. All study treatment materials will be stored in their original packaging in a safe and secure location at the investigational site. Study treatment material will be disposed of in accordance with institutional and/or local requirements.

6.6. INVESTIGATIONAL PRODUCT APPLICATION SCHEDULE

The reconstituted IRDye 800BK Injection solution will be administered to subjects as a onetime dose. A second dose will not be available.

6.7. INVESTIGATIONAL PRODUCT ACCOUNTABILITY

The Investigator or designee will verify the contents of each shipment against the shipping documents. Verification of IP receipt will be documented according to the Sponsor's requirements.

An accountability log will be provided to the site for use by the Investigator to maintain current and accurate inventory records (batch, expiry, and quantity) covering the dispensing and the destruction of the IP.

IRDye 800BK Injection will be administered by trained study staff. Each application of the IP will be recorded in source documents and the eCRF. Study treatment packaging labels with a traceable unique identifier will be saved and available for inspection for Investigational Product accountability throughout the study. At the conclusion of the study the Investigator must return or destroy all IP as instructed by the Sponsor.

6.8. PROHIBITED MEDICATIONS AND THERAPIES

There are no known prohibited medications or therapies during this study.

7. DESCRIPTION OF PROTOCOL ASSESSMENTS AND PROCEDURES

7.1. INFORMED CONSENT

This study will be conducted in accordance with the provisions of the Declaration of Helsinki. A written informed consent will be obtained for this study by the Investigator or designee from all subjects prior to performance of any protocol-specific procedure.

The Investigator must comply with applicable regulatory requirements and must adhere to the Good Clinical Practice (GCP) in the process of obtaining and documenting the informed consent. The Investigator, or designee, must also inform subjects of all pertinent aspects of the study. Before written informed consent is obtained from the subject, the Investigator or a person designated by the Investigator, must provide the subject enough time and opportunity to inquire about the details of the study and to decide whether or not to participate in the trial. All questions addressed by the subject about the study must be answered to the satisfaction of the subject. Prior to the subject's participation in the trial, the written informed consent must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Authorization for release of protected health information must also be obtained, as per local policies.

7.2. ASSESSMENT OF ELIGIBILITY

The Investigator must assess a subject's continued eligibility for the study as per the Inclusion and Exclusion criteria, during the Screening Period. The eligibility criteria are described in Section 3.3. In the event that the subject is not suitable or eligible for the study, the subject will be considered a "screen failure."

If a subject fails initially to meet the eligibility criteria, and is later reconsidered for participation, the subject will be re-consented and assigned a new screening number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened a maximum of one (1) time and

may be enrolled in the study only if they meet all Inclusion and no Exclusion criteria when re-screened.

7.3. DEMOGRAPHIC INFORMATION

In this study, the demographic information will include:

- Dates of ICF signature;
- Date of birth;
- Gender;
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, Caucasian, or other);
- Ethnicity (Hispanic/Latino or Not Hispanic/Latino).

7.4. MEDICAL/SURGICAL HISTORY

A medical/surgical history will be recorded during Screening or, at the discretion of the investigator, during the pre-operative period, and will include:

- All ongoing medical conditions.
- All previously resolved medical conditions that are relevant in the judgment of the Investigator.
- Any prior medical conditions that have resolved within the last year.

Events that emerge prior to administration of IRDye™ 800BK Injection will be recorded as medical history and not as AEs. Aside from being used to determine subject eligibility, this information will permit the Investigator to record the nature, duration, and severity of any ongoing baseline medical conditions prior to the subject's receiving investigational product treatment.

Medical histories will be recorded using the body system categories outlined in Table 7-1 below.

Table 7-1: Medical History Body System Categories

• Cardiovascular	• Lymphatic
• Respiratory	• Hematologic
• Gastrointestinal	• Immunologic
• Renal	• Dermatologic
• Hepatic	• Psychiatric
• Neurological	• Genitourinary
• Endocrine	• Other

For each relevant history, the following will be documented:

- Disease/disorder/condition;
- Date of diagnosis;
- History status (resolved or ongoing).

The subject will be questioned regarding previous surgical procedures and also the current surgical procedure that is scheduled for this study.

7.5. PHYSICAL EXAMINATION

The physical examination will include routine examinations for the following:

- Abnormalities of the female genital tract;
- Head, Ears, Eyes, Nose, Throat (HEENT);
- Abnormalities of the extremities;
- Neurologic abnormalities;
- Heart/cardiovascular abnormalities;
- Musculoskeletal abnormalities;
- Dermatologic abnormalities;
- Any other body system for which an abnormality is noted and which, in the opinion of the Investigator, is relevant to the safety of the subject or could impact safety or efficacy results for the subject; i.e., the abnormality is clinically significant.

Each abnormality will be recorded and the Investigator will record an assessment of its clinical significance.

7.6. VITAL SIGNS, HEIGHT, AND WEIGHT

The following will be collected:

- Vital signs (in the pre-operative holding area, during the procedure, recovery room, and on post-operative day #1):
    - Blood Pressure (taken after the subject has been seated for at least 5 minutes);
    - Pulse;
    - Temperature;
    - Respiratory Rate (not monitored during surgery when the subject's respiratory rate is controlled while on ventilator);
- Height (at screening visit);
- Weight (at screening visit);
- BMI (derived from the height and weight measurements).

7.7. CONCOMITANT MEDICATION

All medications and therapies administered or taken by the subject beginning 30 days prior to the Screening Visit and throughout the study will be recorded in the source documents and on the appropriate page of the eCRF. Subjects must be questioned at each study visit concerning any new medications or changes in current medications including over-the-counter medication and topical medication.

For each medication and non-study treatment, the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown);
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose);

  Note: *Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.*
- Route of dosing;
- Indication for use;
- The start date;
- The stop date (if medication/therapy is not ongoing).

7.8. CLINICAL LABORATORY ASSESSMENTS

Blood samples will be collected for analysis of the following parameters:

- Hematological Parameters: Screening Visit, 12 h Post-Op, and morning of post-operative day #1 (24 h Post-Op).
- Serum Chemistry Parameters: Screening Visit, 12 h Post-Op, and morning of post-operative day #1 (24 h Post-Op).
- Serum pregnancy test (for female subjects of childbearing potential): In the pre-operative holding area.

All laboratory reports will be reviewed by the Investigator. Abnormal results that are considered by the Investigator to be clinically significant (CS) will be recorded as adverse events. If in the Investigator's judgment, in order to make the determination of clinical significance the testing may be need to be repeated. Validated, quality-controlled laboratory data will be transferred to the main database for analyses. See Appendix 1: List of Laboratory Analytes to be tested for each laboratory assessment.

7.9. ELECTROCARDIOGRAM

Resting 12-lead ECGs will be obtained at the Screening Visit and Post-Operative Visits. Results will be evaluated by the Investigator. The following parameters will be recorded:

- Ventricular rate (beats per minute);
- PR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- QTc interval (msec).

Additionally, the investigator will record the overall results of the ECG reading as either normal or abnormal, and as either not clinically significant (NCS) or clinically significant (CS).

Only those subjects who have normal or NCS results will be enrolled in this study.

8. STATISTICAL ANALYSIS

This section presents general information about statistical considerations and concepts and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions that will be used in this study will be in a separate document; i.e., the Statistical Analysis Plan (SAP).

8.1. TREATMENT GROUPS

There will be eight (8) subjects in each cohort; 32 in 3 cohorts in Part A and 16 in 2 cohorts for Part B, for a total of 48 subjects. Each subject will receive one injection of IRDye 800BK Injection solution immediately following confirmation that the laparoscope has been successfully inserted into the abdominal cavity. The starting product dosage (Cohort 1) will be 0.06 mg IRDye 800BK/kg body mass.

The near-optimal dose will be the lowest dose determined to give:

- the highest proportion of subjects that achieve a Ureteral Imaging Score of “4”
- the shortest average time to visualization, and
- the longest average duration of time that the Ureteral Imaging Score remains at least "3"

After each cohort of Part A, the DSMC will review safety data and imaging scores to determine if the trial should continue and that no safety issues have arisen. Barring any safety concerns, the DSMC will review the proportion of subjects that were given a Ureteral Imaging Score of “4," the mean and median times to visualization, the mean and median times that a score of "4" was reached (if at all), and the mean and median times that the Ureteral Imaging Score remained at least a "3." Based on this data, a decision will be made to

- Stop the study because the near optimal dose has been determined
- Continue the study by increasing the dose because improved efficacy is expected, or
- Continue the study by decreasing the dose to determine the lowest fully effective dose.

LI-COR will determine the next dosing level based on recommendations from the PI and the DSMC.

In Part B, each subject will receive IRDye 800BK Injection solution immediately following confirmation that the laparoscope has been successfully inserted into the abdominal cavity. The dose will be the near-optimal dose determined in Part A of the study, and is anticipated to be no greater than 0.12 mg IRDye 800BK/kg body mass. At 10 and 30 minutes (±5 min) images will be captured from the FIREFLY™ imaging system and one additional imaging system (either the Novadaq PINPOINT Endoscopic Fluorescence Imaging System or Stryker Infrared Illuminating System (IRIS) [AIM light source]), depending on cohort. While the images will not be collected simultaneously, the images will be collected within approximately one minute of each other.

The surgeon will score the images for ureter visualization for each image captured as was done in Part A.

8.2. DESCRIPTION OF STUDY OUTCOMES (ENDPOINTS)

8.2.1 Safety Outcome Measures

The safety outcome measurements for the study will be primarily assessed by:

- Evaluation of injection site reactions
- Incidence of Treatment-Emergent serious adverse events (TESAE)
- Incidence of Treatment-Emergent Adverse Events (TEAE)
- Incidence of UADEs related to imaging devices
- Incidence of withdrawals from the study due to TEAEs and/or UADEs
- Changes and shifts in laboratory measurements over time

8.2.2 Efficacy Outcome Measures

The efficacy outcomes for the study will be primarily assessed by:

- Dose response based on the maximum composite assessment of the anatomy and laterality over 90 minutes from infusion, for the detection of the pelvic ureter in women undergoing minimally invasive surgery. This outcome is measured by the composite scales from the following ureteral imaging scales; 0 being the worst and 4 being the best:

  i) Anatomy: Entire ureter length from pelvic brim down (2);
  Partial length (1); or
  No signal visualized (0).

  ii) Laterality: Bilateral (2);
  Right ureter only or Left ureter only (1); or
  None (0).

- Ureter visualization over time by treatment post-infusion from 10 minutes through 90 minutes.
- Anatomical detection of pelvic ureter using ureteral imaging scales (i.e., the entire ureter length from pelvic brim down, partial length, or no signal visualized) over 90 minutes.
- Lateral detection of pelvic ureter using ureteral imaging scales (i.e., bilateral, right or left ureter only, or none) over 90 minutes.

8.3. SAMPLE SIZE DETERMINATION AND RATIONALE

8.3.1 Sample Size

An estimated 48 subjects, eight (8) per cohort, may be enrolled in this trial. The original sample size calculation for this study (N=32) was based on clinical judgment that there will be a large, e.g. at least 70% clinically meaningful difference between the visualization of the highest dose of IRDye 800BK, and the lowest dose. In addition, because the treatment is a single surgical procedure, drop outs are not expected in the study. An additional 16 subjects will be enrolled into Part B, 8 per pairing of imaging devices (Firefly vs PINPOINT; Firefly vs Stryker) to be consistent with the cohorts in Part A. No statistical rationale was used to determine this sample size.

8.3.2 Randomization and Stratification

This is an open-label, multi-cohort dose escalation study, and there is no randomization.

8.3.3 Imaging Cohorts

Subjects in Part B will be enrolled in one of 2 cohorts based on the type of imaging system used in conjunction with the FIREFLY™ system. Eight (8) subjects in each cohort will undergo imaging with either the PINPOINT system or the Stryker AIM system in addition to imaging with the da Vinci Firefly device.

8.4. INTERIM ANALYSIS (IA)

There is no IA for the efficacy in this trial. However, for each cohort, the DSMC will review the safety data collected after all eight (8) subjects, within a dose cohort (Part A) have completed their treatment and completed their follow-up office visit within two weeks of the surgical procedure. In the absence of any safety concerns the DSMC will recommend the next cohort dose.

8.5. GENERAL STATISTICAL CONSIDERATIONS

All collected study data will be presented in subject data listings. The statistical analyses will be performed using SAS® for Windows, Version 9.4 or later. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated by treatment group for continuous variables. Frequencies and percentages will be presented by treatment group for categorical variables.

8.6. ANALYSIS POPULATIONS

The details of the analysis population to be used for the study are described in the below sections. All subjects who are enrolled in the study will be considered for analysis.

8.7.1 Intent-to-Treat (ITT) population

The ITT population is defined as all enrolled subjects. The ITT population will be used for summary of demographics and baseline characteristics.

8.7.2 Efficacy Evaluable (EE) Population

The Efficacy Evaluable (EE) population is defined as all enrolled subjects who received treatment with adequate post baseline efficacy data. This population will be identified before the database lock. The EE population will be used for analyses of efficacy endpoints if it differs from the ITT population.

8.7.3 Safety Population

The Safety population is defined as any subject receiving the treatment after enrollment. This population will be used for the summary of safety parameters.

8.7.4 Covariates

If there are baseline or demographic differences among the cohorts, these may be added as covariates in the dose response analysis of maximum ureter visualization.

8.7. STATISTICAL METHODS

A Statistical Analysis Plan (SAP) will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the efficacy and safety data from this trial.

All inferential statistical analysis will be based on a two-sided test with a Type I error rate of 0.05 or trend analyses where it is applicable. The methodology of the trend analysis will be detailed in the SAP.

All baseline summaries will be performed on the ITT populations. The efficacy analyses presented here will be conducted using EE populations, if it differs from the ITT population. All safety analyses will be conducted using the Safety population.

All data collected will be summarized according to the variable type:

Continuous data summaries will include:

i. For descriptive statistics, the number of observations, mean, standard deviation, median, and minimum and maximum values will be tabulated.
ii. For the inferential statistics Analysis of Covariance (ANCOVA) will be used, with the following points to consider. Due to the small sample size, the Normality assumption of ANCOVA may not be met:
    a. If the Normality assumption is met, ANCOVA using the baseline value as a covariate will be used.

b. If the Normality assumption is not met, a rank–ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data or other non-parametric methods will be used.

Categorical data summaries will include:

i. For descriptive statistics, the frequencies and percentages will be tabulated.
ii. For inferential statistics the Logit model will be used.

8.8. SUBJECT DISPOSITION

The disposition of all subjects who sign an ICF to participate in this trial will be provided. The numbers of subjects screened, enrolled, completed, and discontinued during the study, as well as the reasons for all post-enrollment discontinuations will be summarized by cohort. Disposition and reasons for study discontinuation will also be provided as a by-subject listing.

8.9. DEMOGRAPHICS AND BASELINE CHARACTERISTICS ANALYSIS

Demographics and baseline characteristics will be summarized by cohort (dose given and/or imaging devices) using appropriate descriptive statistics.

8.10. CONCOMITANT MEDICATIONS/THERAPIES

Concomitant medications/therapies will be summarized separately for the Safety population. All prior and concomitant medications recorded in the case report form will be coded to matching Anatomic Therapeutic Classification codes using the most recent version of the WHO Drug Dictionary. Descriptive summaries by cohort will be prepared using the coded term. All concomitant medications/therapies recorded in the case report form will be listed.

8.11. EFFICACY ANALYSIS

The analyses of efficacy outcomes will be conducted on the EE populations, if it differs from the ITT population.

The first efficacy analyses for the study, including the dose-response relationships and trend analyses, will be conducted using the appropriate statistical test on the composite assessment of Anatomy and Laterality data. In addition to the trend analysis for the composite outcome, the data will also be compared between the dose groups using ANCOVA. For all other efficacy outcomes the data will be summarized and compared according to the variable type:

- Continuous data summaries will include:
    - Descriptive summary of number of observations, mean, standard deviation, median, and minimum and maximum values.

- Analysis of Covariance (ANCOVA) for inferential statistics.

- Categorical data summaries will include:
  - Frequency counts and percentages.
  - Logit model for inferential statistics.

8.12. SAFETY ASSESSMENTS

8.13.1 Adverse Events

Adverse events will be coded using the latest version of MedDRA. Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the administration of the treatment. TEAEs will be summarized by dose group, system organ class (SOC), and preferred term (PT). The following TEAE summaries will be provided:

- TEAEs by severity grade;
- TEAEs by relationship to study treatment.

In addition,

- Injection site reactions will be summarized
- Separate summaries of serious adverse events
- Separate summaries of imaging device-related adverse events, including UADEs
- Adverse events resulting in discontinuation of study treatment will be presented

8.13.2 Clinical Laboratory Data

All laboratory values will be listed. Laboratory measurements will also be summarized as continuous variables and presented by dose group.

8.13.3 Other Safety Data

All changes in vital signs will be listed and summarized as change from baseline.

9. ADVERSE EVENTS (DEFINITIONS AND REPORTING)

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs as detailed in this section of the protocol.

9.1. ADVERSE EVENT (AE)

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that occurs or is reported by the patient to have occurred, or a worsening of a pre-existing condition. An adverse event may or may not be related to the study treatment.

AEs will be elicited through direct questioning and subject reports. Any abnormality in physical examination findings or laboratory results that the investigator believes is clinically significant (CS) to the research subject and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant should not be recorded as AEs.

9.1.1 Treatment Emergent Adverse Event (TEAE)

The ICH E9 guidance document defines treatment emergent adverse event as an event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state.

9.1.2 Treatment Emergent Serious Adverse Event (TESAE)

A TESAE is an event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state and can be classified as a SAE as defined in Section 9.9.

9.1.3 Device-related Adverse Event, Including Unanticipated Adverse Device Effect (UADE)

An UADE, as defined under 21 CFR 812.3 (s), is any serious adverse effect on health or safety or 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 investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9.2. REPORTING OF ADVERSE EVENTS

Report initiation for all AEs and SAEs will begin at the time of the IP administration and continue until the end of the final study visit. All events will be followed to resolution or until the subject completes the study. A final assessment of outcome will be made at that time.

All AEs must be recorded in the subject's medical records and in the eCRF. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is considered to be a SAE (see Section 9.9), the impact the event had on study treatment (see Section 9.3), the severity of the event (see Section 9.4), the causality of the event (see Section 9.5), whether treatment was given as a result of the event (see Section 9.6), and the outcome of the event (see Section 9.7).

9.3. IMPACT ON STUDY TREATMENT

The impact the event had on the study treatment will be assessed as either: none, study treatment interrupted, study treatment discontinued, or not applicable. The "not applicable" assessment will be used only when the subject is in the Post-Operative Phase of the protocol.

9.4. SEVERITY ASSESSMENT

The Investigator will carefully evaluate the comments of each subject and the response to treatment in order to judge the true nature and severity of the AE. The FDA toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm) will be used. The investigator will use the AE grading outlined in Table 9-1 for any adverse event not included in the above-mentioned guideline.

Table 9-1: Adverse Event Severity Grading General Guidelines

Grade	Description
Grade 1	Mild; subtle or low intensity; Transient and easily tolerated by the subject.
Grade 2	Moderate; not excessive or extreme; Causes the subject discomfort and interrupts the subject's usual activities.
Grade 3	Severe; intense; Causes considerable interference with the subject's usual activities.
Grade 4	Life threatening or disabling
Grade 5	Fatal

9.5. CAUSALITY ASSESSMENT

AEs will be assigned a relationship (causality) to the study treatment. The Investigator will be responsible for determining the relationship between an AE and the study treatment. The type of event, organ system affected, and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the study treatment. Relationship of AEs to study treatment will be classified as follows:

1. **Definitely related**: This category applies to those AEs that the Investigator feels are

incontrovertibly related to the study treatment. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study treatment; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it follows a known response pattern to administration of the study treatment.

2. **Probably related:** This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study treatment. An AE may be considered probable if or when (must have three): (1) it follows a reasonable temporal sequence from administration of the study treatment; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject; (3) disappears or is decreased upon discontinuation of the study treatment; (4) it follows a known response pattern to treatment with the study treatment.

3. **Possibly related**: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are judged unlikely but cannot be ruled out with certainty to the relationship to the study treatment. An AE may be considered possible if or when (must have two): (1) it follows a reasonable temporal sequence from administration of the study treatment; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject; (3) disappears or is decreased upon discontinuation of the study treatment; (4) it follows a known response pattern to treatment with the study treatment.

4. **Remotely related**: In general, this category can be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are judged likely to be unrelated to the study treatment. An AE may be considered unlikely if or when (must have two): (1) it does not follow a reasonable temporal sequence from administration of the study treatment; (2) it could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject; (3) disappears or is decreased upon discontinuation of the study treatment; (4) it does not follow a known response pattern to treatment with the study treatment.

5. **Unrelated**: This category applies to those AEs which, after careful consideration at the time they are evaluated, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and determined with certainty to have no relationship to the study treatment.

9.6. TREATMENT GIVEN AS A RESULT OF THE EVENT

The event impact in terms of treatment provided will be as either: none, medication administered, non-drug therapy administered, surgery performed, hospitalization, or other (with a specification).

9.7. OUTCOME ASSESSMENT

The outcome of the event will be assessed as either: resolved, resolved with sequelae, ongoing, or death. Only one (1) AE per subject is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given subject, only the primary cause of death will have an outcome of death.

9.8. EXPECTED/ANTICIPATED EVENTS

There is no expected/anticipated event for this IP.

9.9. SERIOUS ADVERSE EVENTS

An SAE is defined as any AE that:

- Results in death;
- Is life threatening (the subject is at immediate risk of dying from the adverse experience);
- Requires subject hospitalization or prolongs existing hospitalization;
- Required medical or surgical intervention to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a device.
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.9.1 Reporting of SAEs and UADEs

The Investigator is required to report all SAEs that occur from infusion of IRDye™ 800BK Injection, as well as all UADEs, through 30 days post-infusion. Once the investigator becomes aware of an SAE or UADE, he/she must report the SAE or UADE within 24 hours to:

SAE FAX number:	(919) 844-6948
SAE e-mail:	saereports@drugsafety.biz
Gil Price, MD:	(240) 426-4695

Dr. Price e-mail: gill.price@propharmagroup.com

The Pharmacovigilance Medical Monitor may request additional supporting documentation as it becomes available, such as lab reports, electrocardiogram reports, discharge summary, hospital notes, etc., if applicable. Additional follow-up information as it becomes available must be reported to the Pharmacovigilance Monitor:

Gil Price, M.D.:	(240) 426-4695
Dr. Price e-mail:	gill.price@propharmagroup.com
SAE FAX number:	(919) 844-6948
SAE e-mail:	saereports@drugsafety.biz

The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

9.9.2 SAE/UADE Follow-Up

All subjects experiencing a SAE and/or UADE, including the discontinued subjects, must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator (i.e., recovery, return to baseline status, no further improvement expected, or death).

For each SAE and/or UADE indicated as an unresolved event on the initial report, regardless of whether the subject completed the study or withdrew, the site should submit a follow-up report with updated information.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Subjects will be identified on CRFs by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject.

The local IRB, FDA, the monitors, auditors, and personnel authorized by the Sponsor are eligible to review the medical and research records related to this study as part of their responsibility to protect human subjects in clinical research. They will be given direct access to source data and documentation, e.g., medical charts/records, printouts, etc., for source data verification, provided that subject confidentiality is maintained in accordance with local requirements. Access to electronic medical records may be governed by institution policy. The University of Alabama at Birmingham site will be required to ensure access while remaining compliant with institutional requirements.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. MONITORING REQUIREMENTS

The specific obligations outlined in 21 Code of Federal Regulations (CFR) and ICH guidelines require the Sponsor to maintain current personal knowledge of the progress of a study. Therefore, the Sponsor's designated monitor will visit the site during the study as well as maintain frequent telephone and written communication. The Investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

The Investigator will permit representatives of the Sponsor and/or designated CRO to inspect all CRFs and corresponding study subject original medical records (source documents) at regular intervals throughout the study. Subject original medical records and other relevant data must be available to support all data recorded in the CRF. In addition to the original medical records, these data may include but are not limited to study laboratory reports, etc.

In accordance with federal regulations, site inspections will serve to verify strict adherence to the protocol and the accuracy of the data that is being entered on the case report forms. A Monitoring Log will be maintained at each study site. The Monitoring Log will be signed by the monitor, dated, and stated the type of visit. The Investigator should be aware that the study site and subject records may be inspected by the Sponsor and or representatives of the designated CRO, FDA or other regional regulatory authority.

11.2. ACCEPTABILITY OF CASE REPORT FORMS (CRFS)

For each subject who has signed an informed consent form, a CRF must be completed. For subjects who are screen failures, this would be limited to the screen failure CRF page. All source documents and CRFs will be completed as soon as possible after the subject's visit and corrections to data on the CRFs will be documented, if applicable. The Investigator will review the CRFs to indicate that, to his/her knowledge, they are complete and accurate. CRFs will be reviewed by the Sponsor’s or designated CRO’s monitor, who will make a decision as to their acceptability.

11.3. MODIFICATION OF PROTOCOL

The Investigator will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator's IRB must also be obtained prior to implementation of the change, with two exceptions:

1. When necessary to eliminate apparent immediate hazard to the subject; or
2. When the modification does not involve the subject's participation in the trial.

An amendment may also require modification of the informed consent form. The Investigator will provide an approval letter for the amendment and revised informed consent form, if applicable, to the Sponsor. An amendment must be provided in writing and it must be dated by both the Sponsor and the Investigator. If necessary, the Sponsor will submit protocol amendments to the FDA and other appropriate regulatory authorities and notify other Investigators using this protocol.

11.4. REPORTING PROTOCOL DEVIATIONS

The Investigator is obligated to follow the protocol without departure from the requirements written in the protocol. If the Investigator deviates from the protocol requirements, the Sponsor will make the determination as to whether the subject will continue in the study. The Sponsor also has the right to discontinue the subject for protocol violations. The IRB may also have to be contacted if safety to the subject or if the scientific soundness of the study is involved. All protocol deviations must be documented in the CRFs.

11.5. MAJOR PROTOCOL DEVIATION OR VIOLATION

A major protocol deviation or violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. Examples of this include:

- Failure to obtain informed consent prior to initiation of study-related procedures.
- A research subject does not meet the protocol's eligibility criteria but was enrolled without prior approval from the Sponsor.
- A research subject received the wrong treatment or incorrect dose.
- A research subject met withdrawal criteria during the study but was not withdrawn.
- A research subject received a prohibited concomitant medication.
- Failure to treat research subjects per protocol procedures that specifically relate to primary efficacy outcomes.
- Changing the protocol without prior Sponsor and IRB approval.
- Multiple minor violations of the same nature after multiple warnings.

11.6. MINOR PROTOCOL DEVIATION OR VIOLATION

A minor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which DOES NOT have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

12. DATA SAFETY MONITORING COMMITTEE (DSMC)

The study will be monitored by an independent DSMC to ensure patient safety and to assess efficacy in the cohorts of Part A. MedSource is responsible for the overall management of the DSMC, including development of its charter and membership selection. The DSMC will be managed in conformance with the FDA guidelines for DSMC independence, management, and oversight.

The DSMC will review safety data and imaging scores of the trial after each cohort. The DSMC will consist of at least three (3) independent members (at least two (2) clinicians with expertise in imaging and one (1) biostatistician) and will review all safety signals including unexpected AEs, all related AEs, all SAEs, and all deaths during the Treatment and Follow-Up Phases.

All expedited safety reports will be provided in real time to the DSMC chair upon being reported to the FDA. The DSMC will make the following recommendations at each safety evaluation:

- Continue the study as planned;
- Modify the study and continue;
- Terminate the study;
- Gather more data to address a specific safety issue and reconvene;
- Other, e.g., request changes to the protocol and propose sanctions.

The Sponsor retains the responsibility to contact the FDA and the final decision regarding the recommendation to continue or to terminate the study.

A further description of the DSMC reporting requirements, meeting frequency, and the study stopping/continuation criteria can be found in the DSMC charter.

13. ETHICS AND REGULATORY REQUIREMENTS

The study will be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with the Declaration of Helsinki, GCP, 21 CFR, ICH E6, HIPAA regulations in 45 CFR Part 164 (US only), and the Belmont Principles of respect for persons, beneficence, and justice. No protocol changes will be implemented without the prior review and approval of the IRB, except when the modification does not involve the subject's participation in the trial or where it may be necessary to eliminate an immediate hazard to a research subject. In the latter case, the change will be reported to the IRB as soon as possible, according to IRB regulations.

Additionally, the study product used in this study is manufactured, handled and stored in accordance with applicable GMP. The study product provided for this study will be used only in accordance with this protocol.

13.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

The Principal Investigator (PI) at the University of Alabama at Birmingham site will provide the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with all appropriate materials as required by their IRB/IEC, including but not limited to the clinical study protocol, informed consent form, and any advertising materials. The study will not be initiated until the IRB/IEC provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The Investigator will not participate in the decision. If the Investigator is an IRB or IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB/IEC as required by local and applicable government regulations and in agreement with policy established by the Sponsor. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB/IEC, and must agree to share all such documents and reports with the Sponsor.

No changes from the final approved protocol will be initiated without the IRB/IEC's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the modification does not involve the subject's participation in the trial.

13.2. INVESTIGATOR'S RESPONSIBILITIES

The Investigator(s) are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations.

Information regarding to the study center participating in this study that cannot comply with these standards will be documented.

13.3. SUBJECT INFORMED CONSENT REQUIREMENTS

All subjects participating in this study will be given to by the Investigator and/or designee, written and oral information about the study in a language understandable by the subject. Written informed consent will be obtained from each subject prior to any procedures or assessments that would not otherwise be required for the care of the subject and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person, e.g., a family member, to be present during the explanation of the study.

The written Informed Consent Form ICF will be in compliance with CFR 21 Part 50.27 and GCP guidelines. The Sponsor and/or designated CRO will approve the ICF and all amendments to the ICF prior to submission to the IRB/IEC. A copy of the ICF to be used will be submitted by the Investigator to the IRB/IEC for review and approval prior to the start of the study. The study site must provide the Sponsor with an unsigned copy of IRB/IEC-approved ICF along with applicable documentation to support this approval. The original signed ICF is retained in the subject's study records, and a copy is provided to the subject. A second copy may be filed in the subject’s medical record, if allowed by institutional policy.

14. DATA HANDLING AND RECORD KEEPING

14.1. RECORDING AND COLLECTION OF DATA

In this study, the primary source document will be the subject's medical record. If separate research records are maintained by the Investigator(s), the medical record and the research records will be considered the source documents for the purposes of auditing the study.

The Investigator will maintain a confidential list of study subjects that will include each subject's study number, name, date of birth, and unique hospital identification number, if applicable. This list will be kept by the Investigator and will not be collected by the Sponsor. A notation will be made in the subject's case history/medical chart that he/she is participating in a clinical study and has provided a signed and dated ICF as well as a release for protected health information as required by local policies. The Investigator must also maintain a separate screening log of all the subjects screened for participation in the study, which should include: gender, age, eligibility status, reason for ineligibility (if applicable), and study allocated subject number (if applicable).

14.2. CLINICAL DATA MANAGEMENT

The Sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the Sponsor's or CRO's standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines, e.g., ICH E6 GCP, and local regulations where applicable, and the Sponsor's or the CRO's SOPs as well as provisions of the study-specific Data Management Plan.

14.3. ARCHIVING

All study documentation at the Investigator's site and Sponsor's site will be archived in accordance with ICH GCP E6 and the Sponsor's quality standards and SOPs.

The Investigator will maintain all research records, reports, and case history reports for a period of two (2) years after regulatory approval of the investigational product. If no application is filed or if the application is not approved, records must be maintained for two (2) years after all investigations have been completed, terminated or discontinued and the FDA has been notified.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or if needed by the Sponsor or its authorized representative (as per GCP 5.5.11).

At the completion of the study, details of the archival process must be provided to the Sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time.

Records to be retained by the Investigator include, but are not restricted to:

- Source data and the primary records upon which they are based, e.g., subject's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the study;
- Completed CRFs;
- Signed protocols and protocol amendments;
- Laboratory results, ranges, and certifications;
- IP and accountability records;
- Study personnel signature log;
- Monitoring logs;
- Correspondence to and from the Sponsor, designee, and IRB;
- Investigator and sub-investigator CVs;
- Signed informed consent and protected health information consent forms;
- Subject screening;
- SAE reports;
- IRB approval and re-approval letters;
- Other documents pertaining to the conduct of the study.

These documents must be maintained and kept on file by the Investigator so that the conduct of the study can be fully documented and monitored.

Study records should not be transferred from site or destroyed without prior written agreement between the Sponsor and the study Investigator. Study records are subject to inspection by applicable health and regulatory agencies at any time.

15. PUBLICATION PLAN

All information supplied by LI-COR, Inc. in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, clinical protocol, case report forms, and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of LI-COR, Inc., shall not be disclosed to others without the written consent of LI-COR, Inc., and shall not be used except in the performance of this study.

It is understood by the Investigator that the Sponsor, LI-COR, Inc., will use the information collected in this clinical trial in connection with the development of IRDye 800BK. Therefore, this information may be disclosed as required to other Investigators or appropriate regulatory authorities. By agreeing to participate in this clinical trial, the Investigator understands that he/she has an obligation to provide the Sponsor with complete test results and all data developed during this trial.

Publication and Disclosure: The site and Investigator(s) agree to submit any proposed manuscript, presentation, or other public disclosure regarding the study to Sponsor for review at least 30 days prior to submitting such proposed manuscript to a publisher, or delivering or making such presentation or other public disclosure to any third party. Within 30 days of its receipt, the Sponsor shall advise the site and/or Investigator, as the case may be, in writing of any information contained therein that is confidential information (other than research results included in a proposed manuscript) or that may impair the Sponsor's ability to obtain patent protection. The Sponsor shall have the right to require the site and/or Investigator, as applicable, to remove specifically identified confidential information (but may not require removal of research results from a proposed manuscript) and/or to delay the proposed submission or delivery of the proposed manuscript or presentation, or other public disclosure, for an additional 60 days to enable the Sponsor to seek patent protection. The site and Investigator shall not publish, publicly disclose, present or discuss any results of or information pertaining to the site's and Investigator's activities prior to completion of the trial, even if the multi-center/single trial or the study is terminated before its completion and the final clinical study report is signed off, or with respect to any endpoints or analyses other than those specified in this protocol.

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17. APPENDIX

17.1. APPENDIX 1: LIST OF LABORATORY ANALYTES

Complete Blood Count

Analyte	Normal Range
White Blood Cells	4.0-11.0 x 10^6/cmm
Red Blood Cells (male)	4.40-5.80 x 10^6/cmm
Red Blood Cells (female)	3.80-5.20 x 10^6/cmm
Hemoglobin (male)	13.5 – 17.0 g/Dl
Hemoglobin (female)	11.3-15.2 g/Dl
Hematocrit (male)	39-50%
Hematocrit (female)	33-45%
Mean Corpuscular Volume	80-96 fL
Mean Corpuscular Hemoglobin	27-33 pg
Mean Corpuscular Hemoglobin Concentration	32-36 g/dL
RBC Distribution Width	11.0-16.0%
Platelet	150-400 x 10^3/cmm
Mean Platelet Volume	8-13 fL

Comprehensive Metabolic Panel

Analyte	Normal Range
Sodium	133-145 mmol/L
Potassium	3.1-5.1 mmol/L
Cloride	97-108 mmol/L
Bicabonate	22-32 mmol/L
Anion Gap	4.0-16.0 mmol/L
Glucose	70-100 mg/dL
Blood Urea Nitrogen	5-22 mg/dL
Creatinine (male)	0.7-1.3 mg/dL
Creatinine (female)	0.4-1.2 mg/dL
Calcium	8.4-10.4 mg/dL
Protein	6.0-8.3 g/dL
Albumin	3.7-5.5 g/dL
Total Bilirubin	0.3-1.4 mg/dL
Alanine Aminotransferase	7-52 units/L
Aspartate Aminotransferase	13-39 units/L
Alkaline Phosphatase	37-117-units/L

Coagulation Panel

Analyte	Normal Range
Prothrombine Time	12.0-14.5 seconds
Partial Thromboplastin Time	25.0-35.0 seconds
INR	2.0-3.0

Urinalysis

Analyte	Normal Range
Color	Yellow, Straw, Amber
Specific Gravity	1.003-1.035
pH	4.6-8.0
Protein	Negative
Ketones	Negative
Glucose	Negative
Blood	Negative
Nitrite	Negative
Leukocytes	Negative
White blood cells	0-5 hpf
Red blood cells	0-2 hpf

17.2. APPENDIX 2 NON-SIGNIFICANT RISK JUSTIFICATION

Non-Significant Risk Justification

IRDye 800BK Background:

LI-COR Inc. (LI-COR) is developing IRDye 800BK (*IND 128269*), a near infrared (NIR) imaging agent for systemically administered staining of ureters and the bladder to allow their structural delineation during surgery. IRDye 800BK NIR imaging agent belongs to a class of heptamethine indocyanines that are characterized by low inherent toxicity, where it will be introduced into surgical patients through intravenous injection and serve as a surgical aid. IRDye 800BK is not intended to be used as a diagnostic imaging agent.

Optical imaging of biological tissues occurs optimally in the NIR region due to excellent tissue penetration of the appropriate light source producing favorable signal-to-background ratios. This is due to minimal auto-fluorescence from biological tissues with minimal scattering and absorption effects. Because the human eye is insensitive to near infrared wavelengths, the use of imaging agents such as IRDye 800BK provides significant practical advantages during surgery.

IRDye 800BK is compatible with camera systems that operate within the near infrared spectral window of 700 to 900 nm. As a surgical aid, IRDye 800BK chemical structure when excited with a light source (e.g., laser, light emitting diode [LED]) emits a photon which can then be detected with the appropriate optical filters and detectors. The number of photons released is dependent upon the amount of energy absorbed by this fluorescent imaging agent.

Proposed Imaging Medical Device Summary:

Currently on the US market, there are multiple FDA cleared surgical NIR imaging systems that would be compatible with IRDye 800BK. Briefly, use of IRDye 800BK requires a fluorescent imaging device with excitation and emission wavelengths in the range of 750-810 nm and 800-850 nm, respectively, utilizing an NIR fluorescence camera systems. All imaging instruments that operate within this spectral range are expected to be compatible with IRDye 800BK.

LI-COR investigated imaging instruments not only based on their specifications, but also on availability of the device for animal studies.

A comparison of critical technical specifications across representative FDA cleared NIR fluorescent imagers demonstrates that these specifications are predominantly conserved. Highlighted below in *Table 2* are the critical technical attributes for the top 4 clinically employed NIR fluorescent imagers; the *Pinpoint Endoscopic Fluorescence Imaging System (510(k) clearance number: K150956)*, *Stryker Infrared Fluorescence (IRF) Imaging System (510(k) clearance number: K142310)*, and the *da Vinci Firefly Imaging System (510(k) clearance number: K141077)*. These critical technical attributes are used by the FDA in the assessment of Substantial Equivalence in the

510(k) clearance of these devices. As illustrated in *Table 2*, the critical technical specifications amongst top clinically utilized imagers are predominantly conserved, where any minor deviations are not anticipated to result in a clinical significance with respect to image quality in the structural delineation of ureters.

Table 2. Comparison of FDA Cleared and Clinically Relevant NIR Fluorescent Imagers

Critical Attributes	**Pinpoint Endoscopic Fluorescence Imaging System**	**Stryker Infrared Fluorescence (IRF) Imaging System**	**da Vinci Firefly Imaging System**
Indications for Use	The PINPOST Endoscopic Fluorescence Imaging System is intended for use to provide real time endoscopic visible and near-infrared fluorescence imaging. The PINPOINT System enables surgeons to perform minimally invasive surgery using standard endoscopic visible light as well as visual assessment of vessels, blood flow and related tissue perfusions, and at least one of the major extra-hepatic bile ducts (cystic duct, common bile duct, or common hepatic duct), using near-infrared imaging. Fluorescence imaging of biliary ducts with the PINPOST System is intended for use with standard of care white light, and when indicated cholangiography. The device is not intended for	The Stryker® IRF Light Source and SafeLight Cable are indicated for use to provide real-time endoscopic visible and near-infrared fluorescence imaging. The Stryker® IRF Light Source and SafeLight Cable enable surgeons to perform minimally invasive surgery using standard endoscopic visible light as well as visual assessment of vessels, blood flow, and related tissue perfusions, and at least one of the major extra-hepatic bile ducts (cystic duct, common bile duct, and common hepatic duct) using near infrared imaging. Fluorescence imaging of biliary ducts with the Stryker® IRF Light Source and SafeLight Cable is intended for use with	The da Vinci® Firefly Imaging System is intended to provide real-time endoscopic visible and near-infrared fluorescence imaging. The da Vinci® Firefly Imaging System enables surgeons to perform minimally invasive surgery using standard endoscopic visible light as well as visual assessment of vessels, blood flow, and related tissue perfusions, and at least one of the major extra-hepatic bile ducts (cystic duct, common bile duct, or common hepatic duct) using near infrared imaging. Fluorescence imaging of biliary ducts with the da Vinci® Firefly Imaging System is intended for use with standard of care white light and,

	standalone use for biliary duct visualization.	standard of care white light and, then indicated, intraoperative cholangiography. The devices are not intended for standalone use for biliary duct visualization.	when indicated, intraoperative cholangiography. The device is not intended for standalone use for biliary duct visualization.
FDA 510(k) Numbers	K150956	K152583	K142310
Manufacturer	Novadaq Technologies, Inc.	Stryker Endoscopy	Intuitive Surgical, Inc.
Approved with Imaging Agent	ICG	ICG	ICG
Scope Diameter	10 mm	10 mm and 5.4 mm	8 mm
Imaging Device	Endoscope	Endoscope	Endoscope
Light Source	Infrared Laser	Infrared Laser	Infrared Laser
Imaging	Fluorescence	Fluorescence	Fluorescence
Angles of View	0 and 30	0 and 30	0 and 30
Excitation Wavelength	805 nm	808 nm	806 nm
Emission Capture	CCD IR Camera	CMOS IR Camera	CCD IR Camera
Display both Visible and IR Images (not necessarily overlapping display)	Yes	Yes	Yes
CCD = Charge coupled device; CMOS = Complementary metal-oxide semiconductor; ICG = Indocyanine green; IR = infrared; NA = Not applicable; NIR = near infrared			

Although the current intended use statement of the imaging medical devices outlined in Table 2 proposed in ongoing clinical study (IND 128269), under *study protocol LICOR-10417-01* does not cover the structural delineation of the ureters, there are no modifications to either the mechanical specifications nor the user protocols required for the imaging and structural delineation of the ureters.

Clinical Expert Opinion:

Clinical expert input from Warner Huh, MD, a surgeon specializing in gynecological procedures, was obtained with respect to the use of various NIR fluorescence platforms in the operating room, where Dr. Warner Huh brought to LI-COR's attention that in clinical practice, the Pinpoint Endoscopic Fluorescence Imaging System can be used interchangeably with the da Vinci Firefly Fluorescent Imager. The da Vinci Surgical System with the Firefly Fluorescent Imaging system, Pinpoint Endoscopic Fluorescence Imaging System and Stryker Infrared Fluorescence (IRF) Imaging System devices are most commonly used for their white light display. In the fluorescence mode, the devices are used to image a similar compound, ICG, for bile duct and other hepatic anatomy. Similarly, based on historical non-clinical data, LI-COR anticipates no visual differences between cleared NIR Fluorescent Imagers, where this class of devices, in conjunction with IRDye 800BK, could be used interchangeably in the structural delineation of the ureters.

Risk Assessment:

The risk determination is based on the proposed use of the imaging devices in conjunction with IRDye 800BK, a compound in the same structural class as ICG, and not on the device alone. The subjects will not need to undergo an additional procedure as part of the investigational study.

NIR wavelengths are low energy and do not pose a risk to the end user, therefore the use of NIR dyes in a surgical setting does not require the use of any special safety equipment for use or viewing in the surgical field.

The protocol is currently enrolling women that will undergo a surgical procedure using the da Vinci robot. These surgeries follow the standard of care on this device. Four to five ports are used for these surgeries. One of these incisions is used as an accessory port, and the additional imaging device (i.e., laparoscope) will be placed in this standard accessory port. The accessory port is placed in all of the patients undergoing robotic surgeries. The accessory port is commonly used to remove fluids, retract tissue or remove specimens with instruments. Therefore, there is little additional risk to inserting the imaging device, as other instruments are routinely inserted into the port. No additional incisions will be required to use these other imaging devices.

The da Vinci Firefly Fluorescence Imager will be used for all surgeries in this protocol. When the second imaging device is inserted into the accessory port, the light source for the da Vinci camera will be switched off. The da Vinci Fluorescent Imager will remain in the port intended for its use, and will be available for use when it is needed again. Even though the da Vinci Firefly Fluorescent

Imager and the Pinpoint Endoscopic Fluorescence Imaging System or Stryker Infrared Fluorescence (IRF) Imaging System will be placed into the patient simultaneously, the two imaging devices are sufficiently separated from one another and there is no risk of damage to either device.

The standard of care for these patients will not be altered based on the images obtained under this protocol. This additional imaging should take two minutes at most and as such, will not prolong the surgery significantly.

Non-Significant Risk Designation:

If a medical device used in a research study is not approved by the FDA for the indication under study, there must be an Investigational Device Exemption (IDE) in place, either granted by FDA (for significant risk devices), or by the IRB (for non-significant risk devices). For research studies using investigational devices (or uses of approved devices outside of their FDA-approved indications), the following requirements requires the submission of either:

a) The FDA-assigned IDE number under the "device" section of the eIRB submission, or

b) Under the device section, information showing that the device is:

- A non-significant risk device, and/or
- Exempt from IDE requirements.

The imaging medical devices proposed in *study protocol LICOR-10417-01* are not significant risk medical devices. FDA defines significant risk devices as follows (21 C.F.R. § 812.3(m)):

"(1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

(2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

(3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

(4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject."

A. Nonsignificant Risk Device (NSR)

Nonsignificant risk devices are devices that do not pose a significant risk to the human subjects. A nonsignificant risk device study requires only IRB approval prior to initiation of the clinical study. Sponsors of studies involving nonsignificant risk devices are not required to submit an IDE application to FDA for approval. Submissions for nonsignificant device investigations are made

directly to the IRB of each participating institution. LI-COR has provided a justification in Appendix A to justify the proposed imaging medical device under *study protocol LICOR-10417-01* for the non-significant risk designation. FDA considers an investigation of a nonsignificant risk device to have an approved IDE when IRB concurs with the nonsignificant risk determination and approves the study.

B. Abbreviated IDE Requirements (21 CFR 812.2(b))

The follow the abbreviated requirements at 21 CFR 812.2(b) must be met to support *study protocol LICOR-10417-01*:

- The abbreviated requirements address labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion
    - Labeling - The device must be labeled in accordance with the labeling provisions of the IDE regulation (§812.5) and must bear the statement "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use."
    - IRB Approval – The sponsor must obtain and maintain Investigational Review Board (IRB) approval throughout the investigation as a nonsignificant risk device study;
    - Informed Consent – The sponsor must assure that investigators obtain and document informed consent from each subject according to 21 CFR 50, Protection of Human Subjects, unless documentation is waived by an IRB in accordance with §56.109(c)
    - Monitoring - All investigations must be properly monitored to protect the human subjects and assure compliance with approved protocols (§812.46). Guidance on monitoring investigations can be found in "Guideline for the Monitoring of Clinical Investigations"
    - Records and Reports - Sponsors are required to maintain specific records and make certain reports as required by the IDE regulation.
    - Investigator Records and Reports – The sponsor must assure that participating investigators maintain records and make reports as required (see Responsibilities of Investigators); and
    - Prohibitions –Commercialization, promotion, test marketing, misrepresentation of an investigational device, and prolongation of the study are prohibited (§812.7)."
- NSR device studies do not have to have an IDE application approved by FDA.
- Sponsors and IRBs do not have to report the IRB approval of an NSR device study to FDA.

- The IRB approves the NSR device study and an investigator may conduct the study without FDA knowing about it.

The IRB serves as the FDA's surrogate for review, approval, and continuing review of the NSR device studies. An NSR device study may start at the institution as soon as the IRB reviews and approves the study and without prior approval by FDA.