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Intraoperative ureter visualization using a near-infrared imaging agent

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Abstract. The fluorescent imaging agent IS-001 was determined to be well tolerated in all subjects and has the potential to provide ureter visualization throughout minimally invasive hysterectomy procedures. This study was conducted to evaluate clinical safety and efficacy of a real-time ureter visualization technique for use during hysterectomy surgery. The study drug appears safe, is renally excreted, and allows enhanced ureter visualization when imaged with a clinically approved near-infrared sensitive endoscope. This is a first-in-human study showing preliminary results that the drug is safe and effective during surgery for improved ureter visualization. [DOI: 10.1117/1.JBO.24.6.066004]

Keywords: ureter imaging; robotic-assisted minimally invasive surgery; near-infrared; hysterectomy.

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1 Introduction

Ureteral injury is a serious complication of gynecological and colorectal surgery that frequently goes unrecognized intraoperatively.[1] Iatrogenic ureteral injury occurs during laparoscopic gynecologic surgery with an incidence of 0.3% to 2.5%[2] with injury rates for high-risk reconstructive pelvic surgeries up to 11%.[3] Only about one-third of ureteral injuries are detected intraoperatively, leading to delayed diagnosis and treatment with deleterious consequences for the patient.[4] Iatrogenic ureteral injury imposes a significant burden in terms of morbidity and increased health care costs and represents a medicolegal challenge for physicians. Sequelae can include fistula and loss of the affected kidney. Risk factors for ureteral injury include the ureter's close proximity to the gynecologic organs within the pelvis, distortion of normal anatomic relationships by pathology such as endometriosis, and surgeon experience.[5] Avoidance of ureteral injury depends upon clear understanding of anatomic relationships and meticulous surgical technique, including careful dissection of pelvic structures.[6]

Minimally invasive surgery (MIS) offers several advantages over traditional open surgical techniques including reduced infection rates, shorter hospital stays, and rapid return to normal activities[7] and is becoming an increasingly more common approach for hysterectomy.[8] One potential drawback to all MIS approaches is an increased risk of inadvertent ureteral injury[7,9] when compared to open techniques.

A variety of renally excreted dyes have been administered in both the preclinical and clinical setting over the past four decades with the goal of ureteral visualization. Indigo carmine,[10] sodium fluorescein,[11] and methylene blue[12,13] have been explored by several groups for use in humans, and a variety of experimental dyes[14–18] have been used in preclinical studies.

Intraoperative near-infrared (NIR) fluorescence imaging is a promising technique that offers real-time visual information about tissues and structures by utilizing wavelengths not visible to the naked eye. One advantage of this in the surgical setting is that visualization of normal tissue is not altered, as is the case with blue dyes and fluorescein. NIR fluorescence imaging in conjunction with the fluorescent dye IS-001 has the potential to provide contrast for improved ureter visualization. In addition, the excitation (peak ~780 nm) and emission (peak ~815 nm) spectra of IS-001 are compatible with clinically available robotic and laparoscopic imaging systems.

2 Study Design and Objectives

The clinical study was performed at Las Palmas Medical Center and the Texas Urogynecology and Laser Surgery Center (El Paso, Texas) between February 2, 2017, and September 9, 2017. All study procedures were reviewed and approved by the Las Palmas Del Sol Healthcare Institutional Review Board (IRB) and conducted under an Investigational New Drug (IND) application with the United States Food and Drug Agency (USFDA) in compliance with Good Clinical Practice (GCP). Signed informed consent was received from all subjects prior to initiation of any clinical study procedure.

This clinical study was designed as a single site, open-label, nonrandomized, dose-escalating study enrolling 24 women aged 18 to 65 undergoing robotic-assisted minimally invasive hysterectomy. Study sample size was based on historical norms for standard phase-1 clinical safety trials. The primary objective of this clinical study was to assess safety and patient tolerance of intravenously (IV) injected IS-001 investigational drug on subjects undergoing robotic hysterectomy. The secondary objective was to evaluate the blood plasma drug pharmacokinetic parameters following IV injection. An additional exploratory objective involved the intraoperative assessment of ureter visibility, fluorescence intensity, and duration.

3 Safety Evaluations and Study Procedures

Subjects were recruited for the study from the investigator's clinical practice and evaluated against the study inclusion and

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Table 1 Inclusion/exclusion criteria.

Study participant criteria
Inclusion criteria
1. Subject is between the ages of 18 and 65
2. Subject is scheduled to undergo robotic hysterectomy using a *da Vinci*® Si/Xi surgical system with Firefly® fluorescent imaging
3. Subject is willing and able to provide informed consent
4. Subject is considered capable of complying with study procedures
5. Subject has no medical history of liver or kidney disease
6. Subject has no evidence of NYHA classes II to IV cardiac disease
7. Subject has recent (<3 months) clinical hematology (CBC) values within the acceptable values reference range [WBC (3.5 to 10.5 K/mm^3) and platelet count (150 to 450 K/mm^3)]
8. Subject has recent (<3 months) clinical serum chemistry (CMP) values within the acceptable values reference range [eGFR (>60 mL/ min /1.73 m^2), ALT (7 to 55 U/L), AST (5 to 40 U/L), ALP (39 to 118 U/L), and total serum bilirubin (0.1 to 1.2 mg/dL)]
Exclusion criteria
1. Subject is pregnant or nursing
2. Subject has a history of alcoholism
3. Subject has a history of drug abuse
4. Subject has known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection
5. Subject has known human immunodeficiency virus (HIV) infection
6. Subject has been diagnosed with or treated for cancer in the last 2 years
7. Subject has a total body weight <32 kg
8. Subject has after 5 min of supine rest a diastolic blood pressure ≥100 mmHg and/or a systolic blood pressure ≥160 mmHg
9. Subject has after 5 min of supine rest a resting heart rate ≤35 or ≥115 bpm
10. Subject has any other condition or personal circumstance that, in the judgment of the investigator, might interfere with the collection of complete good quality data or represents an unacceptable safety liability

exclusion criteria (Table 1). Participants were selected as those scheduled to undergo hysterectomy using a *da Vinci*® Si or Xi surgical system with Firefly® fluorescent imaging for a benign condition. Study procedures followed from a three visit schedule (Table 2), with screening and baseline evaluations [vital signs, 12-lead electrocardiogram (ECG), serum chemistry, serum hematology, and urinalysis (UA)] conducted on visit 1 within ~72-h prior to study drug administration. Visit 2 consisted of 2 days, with hysterectomy and investigational drug administration on day 1, followed by a 24-h postinjection follow-up on day 2. The investigational imaging agent was administered IV as a slow-bolus injection over the course of 1 min. Postdrug 12-lead ECG, serum chemistry, and hematology were performed at ~6-h postinjection on day 1. Intraoperative vital signs were recorded pre- and postinjection. Periodic blood samples were collected preinjection, at 2, 10, 30, and 60 min in addition to 2, 4, and 6 h postinjection for pharmacokinetic drug-plasma analysis. Intraoperative ureter fluorescence visualization observations were made at 10, 30, and 60 min (or last possible timepoint if surgery lasted less than 60 min) postinjection. Images in Firefly® were assessed by the investigator intraoperatively for ureter fluorescence intensity scored on a 4-point scale from 0 to 3, where 0 = none, 1 = mild, 2 = moderate, and 3 = strong fluorescence of the ureter. On day 2 of visit 2, at 24-h follow-up, additional postinjection serum chemistry, serum hematology, and UA samples were analyzed and vital signs were recorded. At visit 3 (14 days ±3 days postinjection), a follow-up consisting of serum chemistry, serum hematology, and UA was performed, and vital signs were recorded. Treatment emergent adverse events were monitored from postinjection through the 14 ± 3 days follow-up until study completion. Safety results were evaluated as shifts from baseline to postinjection and shifts outside the normal reference range. Safety evaluations were tabulated, and based on incidence, clinical significance, and changes in laboratory results but were not statistically powered to detect differences in safety between groups.

4 Pharmacokinetic Assessments and Analysis

Blood samples for pharmacokinetic analysis were collected in potassium EDTA collection tubes. After, blood collection samples were kept on ice until centrifugation. Within 60 min of collection, samples were centrifuged at $3000 \times g$ for 10 min at 4°C, the plasma harvested and aliquoted into plastic tubes, and immediately frozen at −80°C until shipped on dry ice to the central analytical laboratory. Drug-plasma concentrations were analyzed by validated high-performance liquid chromatography and tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantitation (LLOQ) at 0.91 ng/ml. The IS-001 plasma concentration-time data for each subject were analyzed by noncompartmental methods using Phoenix WinNonLin® version 6.2 (Pharsight Corp., Mountain View, California). The noncompartmental analysis provided estimates of the following parameters: plasma concentration at 2 min following the start of the IS-001 IV infusion ($C_{2\text{-min}}$) obtained by log-linear extrapolation of the observed plasma drug concentration-time data, terminal elimination rate constant (λ_z) estimated by linear regression of the terminal exponential component of the log IS-001 plasma concentration–time curve, elimination ($t_{1/2-\lambda z}$) determined by dividing ln (2) by λ_z, the area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0\text{-}\infty}$) obtained by dividing the last observed plasma concentration ≥ lower limit of quantitation by λ_z as the sum of the extrapolated area and $AUC_{0\text{-last}}$, clearance (CL) calculated by dividing the dose by $AUC_{0\text{-}\infty}$, and volume of distribution ($V_{\lambda z}$) estimated by dividing the CL by λ_z.

5 Results

Drug dose assignments followed a sequential, dose escalation design with the first eight subjects receiving a single 10 mg ($n = 8$) IS-001 IV injection, the subsequent eight subjects receiving a single 20 mg ($n = 8$) IS-001 IV injection, and the final eight subjects enrolled receiving a single 40 mg ($n = 8$)

Table 2 Schedule of events.

Activity	Visit 1 screening and admission	Visit 2 study drug administration									Visit 3 follow-up
		Pre	2 min	10 min	30 min	60 min	2 h	4 h	6 h	24 h	14 ± 3 days
Demographics	X										
Inclusion/exclusion criteria	X										
Informed consent	X										
Pregnancy test (if applicable)	X										
Vitals signs	X[a]	X[b]		X[b]		X[b]			X[a]	X[a]	X[a]
Cardiology assessment											
Electrocardiogram (12-Lead ECG)	X								X		
Blood collection procedures											
Serum chemistry panel (CMP)	X								X	X	X
CBC	X								X	X	X
Blood PK sample		X	X	X	X	X	X	X	X		
Urine sample collection procedures											
Urine collection (for safety routine UA)	X									X	X
Additional assessment											
Adverse events monitoring		X	X	X	X	X	X	X	X	X	X
Recording of concomitant medications		X	X	X	X	X	X	X	X	X	
Fluorescence screen capture				X	X	X	X[c]				

X[a]: Awake vital signs (postinjection will be compared to baseline).
X[b]: Anesthesia vital signs (postinjection will be compared to baseline).
X[c]: At latest possible time-point during surgery.

IS-001 IV injection. Figure 1 summarizes the flow of subjects through the screening process to drug-dose cohort. A minimum of 24 h separated individual subjects' dosing to allow for appropriate safety evaluation before a new subject was injected. Dose groups were chosen based on the preclinical safety and pharmacodynamics evaluations of IV IS-001 injection. Dose-cohorts were completed in sequential escalation to allow for full safety evaluation of each dose before a subsequent higher dose was administered. The drug dose-cohort groups had similar baseline characteristics. No placebo was injected, and post-treatment results were compared to pretreatment baseline measurements. IS-001 was injected at the beginning of the hysterectomy procedure when the patient was under anesthesia just prior to robotic endoscope insertion into the abdomen.

Participants were monitored for adverse events (AEs) from investigational drug injection on visit 2 through the 14-day follow-up and end of study. Only treatment emergent adverse events not typically associated with hysterectomy surgery or the surgical recovery process were recorded as AEs. A total of three AEs consistent with this categorization were observed in a total of two subjects, both in the lowest drug-dose cohort (10 mg), none of which were deemed drug related. No further adverse events were observed in any other subject or in any of the escalating drug dose-cohorts. The treatment emergent AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) and listed in Table 3.

All changes in safety-related laboratory parameters observed were consistent with the underlying hysterectomy surgery being performed during study drug administration and the recovery from surgery. No individual change in laboratory parameters was deemed clinically significant. Notable shifts from baseline are provided in Table S1 in the Supplementary Materials, which also shows the mean change from baseline of white blood cell count (WBC) after drug administration and surgery. An increased WBC is consistent with the hysterectomy surgery and recovery.[19,20]

There was no dose-dependent increase in mean change from baseline for WBC, suggesting this effect was not drug related. Mean change from baseline normalized over time to the 14-day recovery. In addition, Table S1 in the Supplementary Materials shows the mean change from baseline of red blood cell count (RBC), percent hematocrit (HCT), and hemoglobin (HgB). The decrease observed in RBC, HCT, and HgB is consistent with surgery and recovery.[21] These values show no dose-dependent increase in mean change from baseline, suggesting the effect was not drug related. The mean changes from baseline

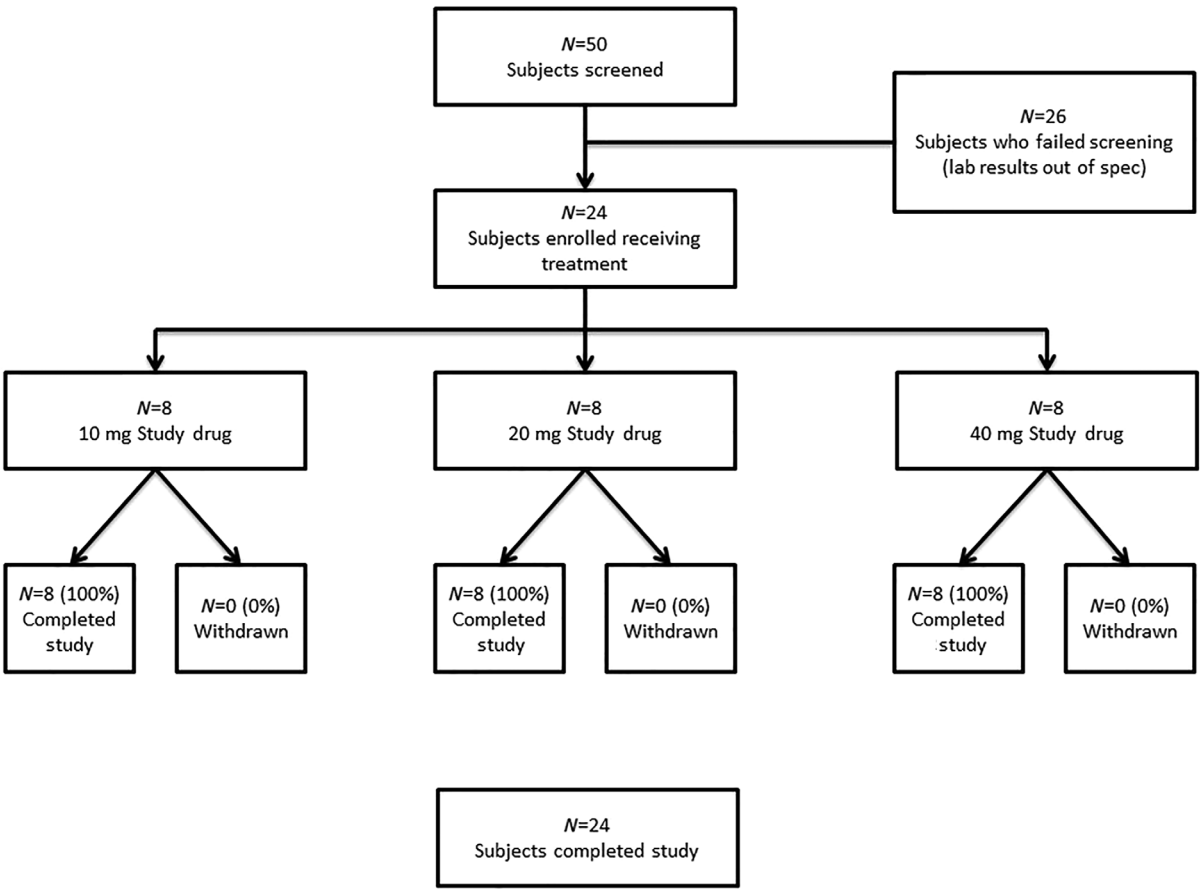

Fig. 1 Disposition of study participants. Of the 50 subjects screened, 26 failed to meet serum chemistry or hematology inclusion criteria. The remaining 24 subjects were assigned to a drug dose-cohort in an escalating fashion based on their enrollment in the study.

normalized over time to the 14-day recovery visit. Changes in serum albumin and calcium were also observed and are shown as mean change from baseline. A decrease in serum albumin[22] and serum calcium[23] is consistent with surgery and recovery. These values show no dose-dependent increase in mean change from baseline, suggesting the effect was not drug related. These mean changes from baseline normalized over time to the 14-day recovery visit. Table S2 in the Supplementary Materials shows the laboratory value shifts outside of the normal reference range as fraction of subjects. An additional observed increase was seen in a fraction of participants presenting with occult blood in urinalysis [10 mg–baseline (1/8), 24 h (8/8), 14 day (4/8), 20 mg–baseline (2/8), 24 h (7/8), 14 day (3/8), 40 mg–baseline (4/8), 24 h (7/8), 14 day (3/8)]. These results are also consistent with hysterectomy surgery and insertion and removal of the foley catheter.[24] These incidence values show no dose-dependent increase, suggesting the effect was not drug related. No other notable change was seen in any other laboratory parameter including 12-lead ECG (QTc) or vital sign measurements.

Table 3 Treatment emergent adverse events by preferred term.

Treatment emergent adverse events by MedDRA[a] preferred term		
Total number of subjects	24	
Total number of adverse events	4	
Number of subjects (%) reporting ≥1 treatment-emergent event	*n*	%
Nervous system disorders > headache (10019211)	1	4.5
Renal and urinary disorders > urinary tract infection (10046571)	1	4.5
Musculoskeletal and connective tissue disorders > neck pain (10028836)	1	4.5
Injury, poisoning, and procedural complications > medical device site pain (10076133)	1	4.5

[a]Medical dictionary for regulatory activities.

Six hours after IV administration, drug-plasma levels were at or near the limit of quantitation (0.91 ng/ml) (Table 4). Pharmacokinetic analysis shows that IS-001 plasma concentrations decline in a biexponential pattern following IV administration. Plasma elimination is rapid with mean terminal half-life ($t_{1/2\text{-}\lambda z}s$) ranging from 0.5 to 2.5 h (Table 5).

Intravenous injection of IS-001 produced ureter fluorescence when imaged with the *da Vinci*® Surgical System's Firefly® fluorescent imaging at all tested doses as shown in Fig. 2. The 40-mg dose-cohort showed the strongest ureter fluorescence at all time-points evaluated postinjection as assessed by the operating surgeon. At 10 min postinjection, the 40-mg dose-cohort showed the highest fluorescence intensity with ureter images in

Table 4 IS-001 plasma concentrations.

		IS-001 plasma concentrations (ng/mL)							
Dose (mg)	Time	Predose	2 min	10 min	30 min	60 min	120 min	240 min	360 min
10	Mean	BQL[a]	2676	614	95.1	39.4	12.4	2.9	2.7
	CV[b]%	BQL[a]	25.6%	48.9%	55.5%	122.2%	170.6%	127.4%	75.8%
	Median	BQL[a]	2395	536	92.1	20.3	4.6	1.4	1.6
	Range	BQL[a]	2055 to 3981	259 to 1086	34.5 to 195	13.3 to 156	2.0 to 64.4	0.9 to 11.7	BQL[a] to 6.0
20	Mean	BQL[a]	3608	768	253	148	47.8	5.3	4.8
	CV[b]%	BQL[a]	22.8%	51.5%	156.7%	222.4%	203.1%	184.2%	163.0%
	Median	BQL[a]	3739	668	100	21.0	7.8	2.0	1.3
	Range	BQL[a]	1977 to 4693	323 to 1548	50.4 to 1215	12.2 to 960	4.0 to 284	1.2 to 29.2	BQL[a] to 18.9
40	Mean	BQL[a]	7627	1838	163	60.3	13.9	4.4	2.2
	CV[b]%	BQL[a]	36.6%	52.2%	57.2%	50.9%	40.3%	26.3%	53.1%
	Median	BQL[a]	7194	1764	156	47.9	12.9	4.1	1.8
	Range	BQL[a]	3782 to 11,792	368 to 3349	61.5 to 342	24.0 to 115	7.7 to 25.7	3.1 to 6.5	1.2 to 4.6

[a]Below quantitative limit.
[b]Coefficient of variation.

Table 5 Pharmacokinetic parameters following single IV infusion.

		Pharmacokinetic parameters					
Dose (mg)	Label	$C_{2\text{-min}}$[a] (ng/ml)	$AUC_{0\text{-}\infty}$[b] (h-ng/ml)	Cl[c] (ml/min/ 1.73 m^2)	$V_{\lambda z}$[d] (l/kg)	λ_z[e] (1/h)	$t_{1/2\text{-}\lambda z}$[f] (h)
10	Mean	2676	534.1	309	0.5	0.569	1.47
	CV%	25.58%	32.66%	26.3%	59.3%	44.8%	49.2%
	Median	2395	485.7	297	0.4	0.595	1.18
	Range	2055 to 3981	331.5 to 877.4	177 to 442	0.2 to 1.2	0.275 to 0.955	0.73 to 2.52
20	Mean	3608	944.3	400	0.5	0.731	1.02
	CV%	22.8%	74.0%	35.7%	48.1%	33.9%	25.1%
	Median	3739	730.4	390	0.5	0.664	1.05
	Range	1977 to 4693	542.1 to 2661.0	115 to 626	0.1 to 0.9	0.522 to 1.293	0.54 to 1.33
40	Mean	7627	1490.4	470	0.7	0.560	1.31
	CV%	36.6%	37.7%	45.6%	50.1%	22.6%	31.2%
	Median	7194	1451.2	412	0.5	0.551	1.26
	Range	3782 to11,792	641.9 to 2297.8	214 to 881	0.5 to 1.4	0.306 to 0.685	1.01 to 2.27

[a]IS-001 plasma concentration at 2 min from the start of the IV injection.
[b]Area under the plasma concentration-time curve from time 0 to infinity.
[c]Clearance.
[d]Volume of distribution.
[e]Terminal elimination rate constant.
[f]Elimination half-life.

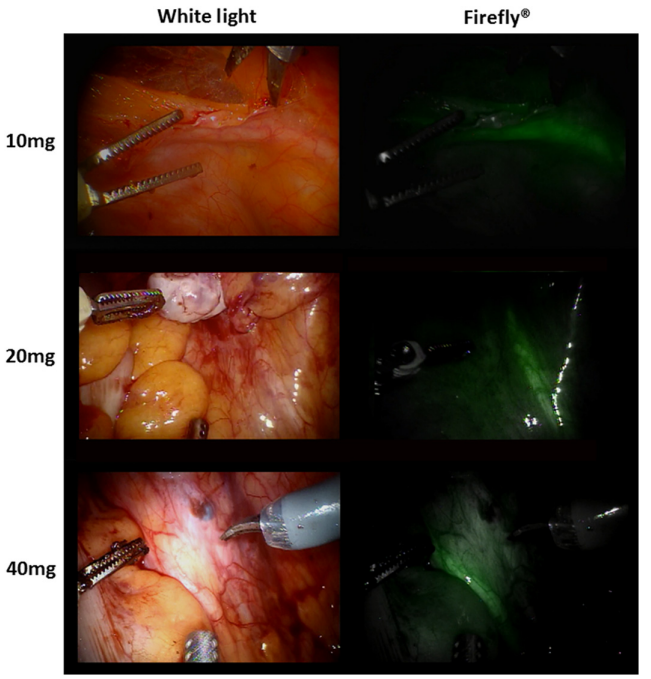

Fig. 2 Ureter near-infrared fluorescence following IV IS-001 injection. Intraoperative white light and near-infrared Firefly® images of the ureter during *da Vinci®* hysterectomy ~20 min after IV IS-001 injection at 10, 20, or 40 mg per patient.

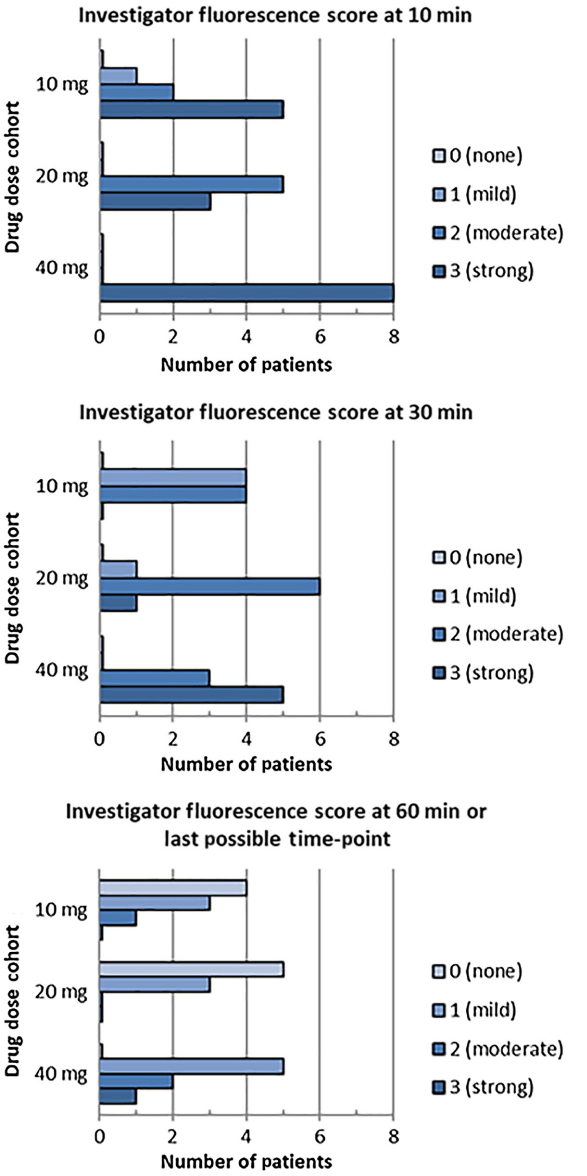

Fig. 3 Intraoperative ureter fluorescence scores. Surgeon-assessed intraoperative ureter fluorescence scores. Assessments were made at 10, 30, and 60 min (or last possible time-point if surgery lasted less than 60 min) postinjection ($n = 8$ for each dose-cohort at each time-point). Images in Firefly® mode scored for ureter fluorescence intensity scored on a 4-point scale from 0 to 3, where 0 = none, 1 = mild, 2 = moderate, and 3 = strong fluorescence of the ureter.

Firefly® mode from all eight subjects (8/8) being scored 3 (strong fluorescence), compared with three of eight (3/8) in the 20 mg and five of eight (5/8) subjects in the 10-mg dose-cohort (Fig. 3). At 30 min postinjection, ureter images in Firefly® mode from five of eight (5/8) subjects in the 40-mg dose-cohort scored 3 (strong fluorescence) relative to one of eight (1/8) in the 20-mg dose-cohort and none of eight (0/8) in the 10-mg dose-cohort. At the 60 min postinjection (or last possible time-point if the surgery duration was shorter than 60 min) fluorescence intensity was diminished relative to the earlier time-points in all dose-cohorts. Images in Firefly® mode from one of eight (1/8) subjects in the 40-mg dose-cohort scored 3 (strong fluorescence) relative to none of eight (0/8) in both the 10- and 20-mg dose-cohorts. However, some fluorescence (a score of 1 or greater) was seen in Firefly® mode images from all eight of eight (8/8) subjects in the 40-mg dose-cohort at this time-point, whereas Firefly® mode images from four of eight (4/8) subjects in the 10-mg dose-cohort and five of eight (5/8) subjects in the 20-mg dose-cohort scored 0 (no fluorescence) (Fig. 3).

Ureter-to-background signals are shown in Fig. 4. Briefly, representative regions of interest within the ureter and ~5 cm away from the ureter were used to compute this ratio for all dose cohorts and all time points. This was an exploratory endpoint, and the differences between dose cohorts were not statistically significant.

6 Discussion

Iatrogenic ureteral injury remains a severe complication of pelvic surgery that imposes a significant burden in morbidity and health care cost. Approximately 600,000 hysterectomies[25] and 300,000 colon surgeries[26] are performed annually in the United States. The estimated ureteral injury rates in hysterectomy and colorectal surgery have been reported anywhere between 0.3% to 2.5%[2,27,28] and 0.2% to 7.6%, respectively.[29] With an average hospital stay of ~4 days and an average cost of $31,000 per ureteral injury,[30] the economic impact in the United States alone approaches $1.1B annually.

Avoidance of ureteral injury depends upon clear understanding of anatomic relationships, meticulous surgical technique, and the ability to visually identify the ureter and distinguish it from surrounding structures. Frequently, this requires careful retroperitoneal dissection and surgical ureterolysis. Current methods for intraoperative ureter visualization include ureteral stent placement with palpation,[31] illuminated catheters,[32] x-ray fluoroscopy with iodine contrast,[33] or dye injections,[34–37] techniques that come with significant additional risk to the patient, operating room workflow issues or lack the required sensitivity.

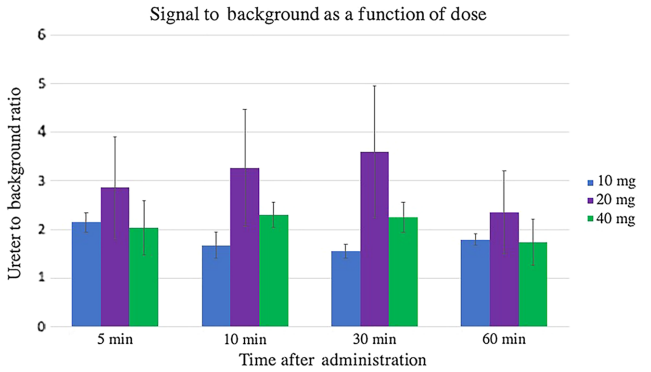

Fig. 4 Green pixels in regions of interest within the ureter and 5 cm away from the ureter were used to compute a ureter-to-background ratio. While the results were not statistically significant, trends generally indicate a drop off in signal beyond 30 min.

Each of these techniques requires surgical training and privileging beyond the scope of most gynecologic and colorectal surgeons, necessitating intraoperative consultation with urology or urogynecology. A potential advantage of an intravenously administered, renally excreted fluorophore such as IS-001 is that it bypasses this cumbersome requirement, eliminates prolonged operating room delays, and improves surgical workflow.

This first-in-human clinical study supports the safety and tolerability of IV IS-001 injection for fluorescent ureter visualization to doses of up to 40 mg per participant. The four adverse events recorded during this study in two subjects included headache, neck pain, urinary tract infection, and device site pain and were not deemed related to IS-001 (Table 3). All AEs were seen only in the lowest dose cohort (10 mg) and were not observed in the escalating dose-cohorts (20 and 40 mg).

Similarly, observed changes in laboratory parameters Table S1 in the Supplementary Materials are consistent with what is reasonably expected after hysterectomy surgery. The increased WBC[19,20] and decrease in RBC, HCT and HgB,[21] serum albumin,[22] and serum calcium[23] is consistent with observed changes following routine surgery and shows no dose-dependent increase in mean change from baseline, suggesting this effect was not drug related. The mean change from baseline normalized over time to the 14-day follow-up time-point. The observed increase in microscopic hematuria noted after surgery is consistent with bladder catheterization and hysterectomy surgery.[24]

The pharmacokinetic analysis shows that IS-001 is rapidly cleared from the blood, limiting unnecessarily prolonged drug exposure when ureter visualization is no longer required, with most subjects reaching the limit of detection of drug in blood plasma by 6-h postinjection (Table 4).

Fluorescent ureter visualization was observed in all subjects following IV infusion of IS-001 when imaged with the *da Vinci*® Surgical System's Firefly® fluorescent imaging at all tested doses (Fig. 2). The 40-mg dose-cohort showed the strongest ureter fluorescence at all time-points evaluated postinjection (Fig. 3) when assessed by the operating surgeon.

The intention of this study was to determine the first-in-human safety and tolerability of IS-001 and establish its pharmacokinetic profile. As a phase I study designed to assess the safety and tolerability of IS-001, this study was not randomized, controlled, or powered to detect differences in ureteral injury at escalating doses. Having detected no drug-related adverse events across all dose cohorts studied and with PK data showing virtually complete elimination at 6 h at all doses, this study suggests an adjunctive role for IS-001 as a complement to careful surgical technique to facilitate ureteral identification during gynecologic and colorectal surgery. Further study is required to test this hypothesis. The current study looked only at a small group of female patients undergoing straightforward robotic hysterectomy by a single surgeon who rated ureteral fluorescence visualization according to a subjective scale. Participants were overwhelmingly Caucasian, Hispanic, and of middle age, and future studies should expand the demographic scope. Further, the current study considers ureteral visualization only at the pelvic brim, where the ureter can often be seen transperitoneally without use of adjunctive tools to enhance visualization. Future studies should assess ureteral visualization in areas of the pelvis where transperitoneal visualization is not as easily achieved and employ objective means to evaluate intensity of ureteral fluorescence to help elucidate the optimal drug dose and dosing schedule. The current study provides evidence that IV IS-001 shows acceptable early safety and tolerability, provides ureter fluorescence when activated by near-infrared light (Firefly® mode) with higher fluorescence scores at escalating doses. This suggests a potential role for IS-001 in gynecologic and colorectal surgery that future studies designed to account for these limitations can better define.

Disclosures

Alwin Klaassen disclosed the following—Intuitive Surgical: Employment, ownership interest includes stock, stock options, patent, or other intellectual property. Jonathan Sorger disclosed the following—Intuitive Surgical: Employment, ownership interest includes stock, stock options, patent, or other intellectual property. Richard Farnam—Intuitive Surgical: Proctoring and travel fees. Richard Arms—none.

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