A Phase 2 Randomized Open-Label Dose-Ranging Study for Ureter Visualization, Using Pudexacianinium Chloride (ASP5354) in Subjects Undergoing Minimally Invasive Colorectal Surgery

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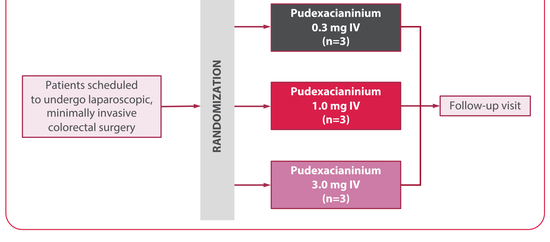
BACKGROUND

- Iatrogenic ureteral injury (IUI) is a rare but serious and life-threatening intraoperative complication of abdominopelvic surgeries if not identified and adequately managed[1]
- Identifying the ureters during surgery can be challenging, especially in patients with advanced endometriosis, inflammatory disease, cancer, previous surgery, or radiotherapy[2,3]
- Although preoperative ureteral stenting may help identify the ureters and avoid IUI, this procedure is invasive, associated with complications, and does not significantly reduce injury rate; intravenous (IV) or retrograde pyelography and urologic computed tomography can be used to help avoid injury but do not provide real-time guidance during the surgical procedure[4-7]
- Therefore, effective, noninvasive, and safe imaging techniques are needed for real-time anatomical ureter visualization during surgery
- Pudexacianinium chloride (ASP5354) is an indocyanine-green (ICG) derivative with hydrophilic properties and therefore rapid, near-complete urinary clearance without metabolism after IV administration, enabling accurate ureter visualization[8]
- In a phase 1, double-blind, randomized, placebo-controlled study in healthy volunteers, single IV administration of pudexacianinium up to 24 mg was considered safe and well tolerated; urinary excretion was rapid and nearly complete, with 77-100% excreted unchanged[9]
- This phase 2 study was performed to determine the optimal dose of pudexacianinium for ureter visualization after IV administration in subjects undergoing laparoscopic, minimally invasive colorectal surgery

METHODS

- This was a phase 2, randomized, open-label, dose-ranging clinical trial in adult participants scheduled to undergo laparoscopic, minimally invasive colorectal surgery
- Eligible participants were aged ≥18 years with adequate liver, renal, and bone marrow function
- Patients with a history of retroperitoneal fibrosis, active urinary tract infection, previous exposure to pudexacianinium, or hypersensitivity to pudexacianinium or ICG were excluded
- Patients were randomized to receive a single intraoperative IV dose of 0.3-mg, 1.0-mg, or 3.0-mg pudexacianinium (**Figure 1**)
  - All dose levels and concentrations are expressed as pudexacianinium free base

Figure 1. Study Design



- The primary endpoint was successful intraoperative ureter visualization, defined as anatomical visualization of the index ureter 30 minutes after pudexacianinium administration and at the end of surgery using a Stryker 1688 AIM device
  - Quantitative assessment of fluorescence intensity was performed using ImageJ[10] which calculates a color contrast value between the inside and outside of the ureter. Fluorescence intensity was quantified by comparing values before and after pudexacianinium administration
  - A Visualization Review Committee (VRC) consisting of the investigators and the sponsors' medical and safety representatives assessed dose levels based on factors including anatomical visualization and fluorescence intensity using the Likert scale
- Secondary objectives included safety and pharmacokinetics, including treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), change from baseline in electrocardiogram parameters, and pharmacokinetics (plasma and urine concentrations of pudexacianinium and its excretion in urine)
- Exploratory endpoints included fluorescence intensity during surgery, duration of index ureter visualization, and visualization of contralateral ureter
- Data were summarized with descriptive statistics by dose group

RESULTS

Patients

- Of 16 subjects enrolled, nine were treated with pudexacianinium 0.3 mg, 1.0 mg, and 3.0 mg (n=3 for each of the three dose levels) and included in this analysis (six subjects failed screening and one was not treated)
- Median age was 53 years (range: 24-69 years) and 7/9 (77.8%) patients were female (**Table 1**)

Table 1. Patient Demographics

	Pudexacianinium		
	0.3 mg (n=3)	1.0 mg (n=3)	3.0 mg (n=3)
Age, years, median (min, max)	55 (53, 58)	55 (46, 69)	45 (24, 46)
Female, n (%)	3 (100)	2 (66.7)	2 (66.7)
Race, n (%)			
White	2 (66.7)	3 (100)	3 (100)
Black or African American	1 (33.3)	0	0
Hispanic or Latino, n (%)	1 (33.3)	2 (66.7)	1 (33.3)
Weight, kg, mean (SD)	68.2 (21.8)	87.2 (10.2)	68.4 (20.4)
BMI, kg/m^2			
Mean (SD)	26.7 (10.0)	29.3 (3.5)	26.8 (7.1)
Min, max	19.4, 38.1	25.6, 32.5	18.7, 32.1

Abbreviations: BMI, body mass index; SD, standard deviation.

Efficacy

- All three doses of pudexacianinium provided enhanced anatomical visualization of ureters (**Table 2, Table 3**)
- Analysis of the primary endpoint showed that successful intraoperative ureter visualization occurred at 30 minutes after dosing and at the end of surgery for 3/3 patients who received pudexacianinium 1.0 mg or 3.0 mg and 2/3 patients who received the 0.3-mg dose (**Figure 2, Figure 3, Table 2**)
- The median fluorescence intensity values based on investigator assessment were 1 (mild) in the 0.3-mg dose group, 2 (moderate) in the 1.0-mg dose group, and 3 (strong) in the 3.0-mg dose group (**Figure 3, Table 2**)
- The quantitative assessment revealed a difference in color contrast ratios of 0.93 between the 0.3-mg and 1.0-mg dose groups and 0.16 between the 1.0-mg and 3.0-mg dose groups (**Table 2**)
- In the exploratory analysis, continuous fluorescent ureter visualization during the entire procedure was assessed as a significant clinical benefit by study surgeons (**Table 3**)

Table 2. Detailed Index Ureter Visualization and Quantitative Results

Pudexacianinium Dose	Sex	Age (y)	BMI (kg/m^2)	Surgery Type	Index Ureter	Ureter Visualized		Intensity Score[a]		Quantification of Color Contrast	
						30 min	End	30 min	End	With Dye Average	Without Dye Average
0.3 mg	F	53	22.6	Total colectomy	R	Yes	No	1	0	1.96	1.06
	F	58	19.4	Hemicolectomy (R)	R	Yes	Yes	2	1	1.65	1.07
	F	55	38.1	Hemicolectomy (R)	R	Yes	Yes	1	1	2.36	1.4
								Mean contrast[b]		**1.99**	**1.17**
1.0 mg	F	55	29.9	Lower ant. resection	L	Yes	Yes	2	2	2.86	1.06
	M	46	25.6	Sigmoid resection/ lower ant. resection	L	Yes	Yes	2	2	2.31	1.06
	F	69	32.5	Hemicolectomy (R)	R	Yes	Yes	3	3	3.60	1.10
								Mean contrast[b]		**2.92**	**1.07**
3.0 mg	F	46	32.1	Hemicolectomy (R)	R	Yes	Yes	3	3	4.35	1.18
	M	45	29.5	Proctocolectomy	L	Yes	Yes	3	3	2.77	1.06
	F	24	18.7	Total colectomy	R	Yes	Yes	3	3	2.14	1.12
								Mean contrast[b]		**3.08**	**1.12**

[a]0=none; 1=mild; 2=moderate; 3=strong.
[b]Average green/(red+blue) contrast value based on quantification assessment.
Abbreviations: BMI, body mass index; F, female; L, left; M, male; R, right

Table 3. Clinical Benefits of Visualization by Pudexacianinium During Surgery

Number Answering "Yes," (%)	Pudexacianinium		
	0.3 mg (n=3)	1.0 mg (n=3)	3.0 mg (n=3)
The location of the index ureter was as expected	3 (100)	3 (100)	3 (100)
Visualization of the index ureter occurred with white light 30 min after pudexacianinium administration	3 (100)	3 (100)	3 (100)
Visualization of the index ureter occurred with white light at the end of surgery	1 (33.3)	3 (100)	3 (100)
NIR-F was superior to white light in terms of visualization of the index ureter	2 (66.7)	3 (100)	3 (100)
The location of the ureter visualized by NIR-F did not alter the operative plan	3 (100)	3 (100)	3 (100)
No ureter anomalies or abnormalities were observed	3 (100)	3 (100)	3 (100)

Abbreviation: NIR-F, near-infrared fluorescence.

Figure 2. Index Ureter Visualization at 30 Minutes Post Pudexacianinium Administration and at End of Surgery

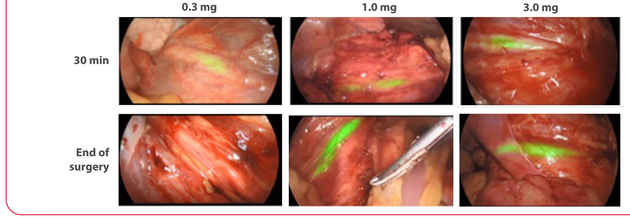
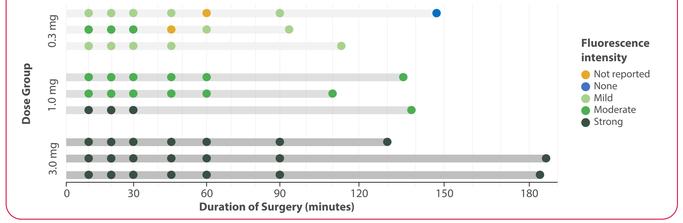


Figure 3. Fluorescence Intensity of the Index Ureter at Each Time Point During Surgery



Safety

- Five (55.6%) patients experienced TEAEs, none of which were considered related to pudexacianinium (**Table 4**)
- Two (22.2%) patients experienced SAEs, neither of which were considered related to pudexacianinium
  - One patient experienced perforation of the rectal stump for which histology was positive for colon cancer (coded as rectal perforation and colon cancer)
  - One patient experienced blood loss anemia
- No deaths occurred during the study
- Minor changes from baseline in QTcF (corrected QT interval using Fridericia's formula) were observed in all patients during the postoperative period; values reverted to baseline (change ≤0 msec) for six (66.7%) participants, and three (33.3%) experienced changes of ≤30 msec[1]

Table 4. Safety Summary

n (%)	Pudexacianinium			Total (N=9)
	0.3 mg (n=3)	1.0 mg (n=3)	3.0 mg (n=3)	
TEAE	2 (66.7)	2 (66.7)	1 (33.3)	5 (55.6)
Drug-related AE	0	0	0	0
Serious AE	2 (66.7)	0	0	2 (22.2)
Worst grade ≥3 AE	2 (66.7)	0	0	2 (22.2)
Deaths	0	0	0	0
TEAEs by organ class				
Blood and lymphatic system disorders, n (%)	1 (33.3)	0	0	1 (11.1)
Blood loss anemia[a]	1 (33.3)	0	0	1 (11.1)
Gastrointestinal disorders, n (%)	1 (33.3)	0	1 (33.3)	2 (22.2)
Abdominal rigidity	0	0	1 (33.3)	1 (11.1)
Rectal perforation[a]	1 (33.3)	0	0	1 (11.1)
Injury, poisoning, procedural complications, n (%)	0	2 (66.7)	0	2 (22.2)
Incision site erythema	0	1 (33.3)	0	1 (11.1)
Procedural nausea	0	1 (33.3)	0	1 (11.1)
Procedural pain	0	1 (33.3)	0	1 (11.1)
Musculoskeletal and connective tissue disorders, n (%)	1 (33.3)	0	0	1 (11.1)
Muscle spasms	1 (33.3)	0	0	1 (11.1)
Neoplasms benign, malignant, and unspecified, n (%)	1 (33.3)	0	0	1 (11.1)
Colon cancer[a]	1 (33.3)	0	0	1 (11.1)

[a]Serious TEAE unrelated to treatment.
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

Pharmacokinetics

- Plasma pudexacianinium concentrations were dose-dependent, but slightly less than dose-proportional (**Table 5**)
- Urinary excretion of pudexacianinium was confirmed in the study: 22.3% to 39.5% of the administered dose was excreted as unchanged in urine during surgery

Table 5. Pudexacianinium Plasma Concentration Over Time and Total Urine Excretion During Surgery

	Pudexacianinium		
	0.3 mg (n=3)	1.0 mg (n=3)	3.0 mg (n=3)
Plasma concentration, ng/mL, mean (SD)			
Predose	0 (0)	0 (0)	0 (0)
10 min	48.9 (20.6)	196 (161)	322 (177)
30 min	22.5 (3.3)	58.0 (5.7)	146 (46.1)
60 min	15.3 (N/A)[a]	38.2 (7.4)[b]	106 (N/A)[a]
90 min	12.7 (N/A)[a]	34.4 (N/A)[a]	NR
120 min	8.4 (N/A)[a]	NR	NR
End of surgery	14.0 (6.0)	28.0 (1.6)	47.3 (29.8)[b]
180 min	NR	18.0 (N/A)[a]	NR
Pudexacianinium excreted in urine, mean (SD)			
mg	0.067 (0.024)	0.212 (0.034)	1.19 (0.37)
%	22.3 (8.0)	21.2 (3.4)	39.5 (12.4)

[a]n=1.
[b]n=2.
Abbreviations: N/A, not applicable; NR, not reported (n=0); SD, standard deviation.

Optimal dose determination

- Based on the totality of the data (and the three dose levels evaluated), the VRC selected 1.0-mg pudexacianinium as the minimally effective dose based on more favorable findings than 0.3 mg and similar findings to 3.0 mg

CONCLUSIONS

- Results of this phase 2, dose-ranging study showed that IV administration of pudexacianinium enhanced anatomical visualization of the ureter under near-infrared fluorescence conditions at all doses administered
  - The enhancement of ureter visualization was sustained for the duration of surgery at both 1.0-mg and 3.0-mg doses
  - Investigator satisfaction was high: the continuous fluorescent visualization of the ureters throughout the procedures was perceived as a significant advantage by both study surgeons
- Pudexacianinium appeared to be safe and well tolerated
  - No TEAEs or SAEs were considered related to pudexacianinium administration; the two SAEs that occurred were mostly consistent with colorectal surgery
- Visualization data, aligned with the pharmacokinetic findings, revealed a dose-dependent increase of plasma and urine pudexacianinium concentrations
  - 22.3% to 39.5% of the administered pudexacianinium was excreted unchanged in urine during surgery (period) across the tested dose range
- The findings of this study indicate that 1.0-mg pudexacianinium is the minimally effective dose for interoperative ureter visualization

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