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RESEARCH

Effects of renal impairment on the pharmacokinetics, safety, and tolerability of pudexacianinium (ASP5354) after IV administration: a mechanistic exploration

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Abstract

Purpose To elucidate mechanisms of renal excretion of pudexacianinium (ASP5354) and evaluate renal impairment effects on pharmacokinetics, safety, and tolerability of pudexacianinium.

Methods Transcellular transport and transporter-mediated uptake of pudexacianinium were investigated in cells expressing human renal drug transporters P-gp, BCRP, OAT1, OAT3, OCT2, MATE1, and MATE2-K. A Phase 1, open-label, parallel-group study ($N=28$) was conducted in 6 participants each with mild, moderate, and severe renal impairment; 10 with normal renal function. Participants received a single intravenous dose of pudexacianinium 3 mg. Plasma and urine were collected post-dosing for pharmacokinetics.

Results In vitro, pudexacianinium was not a substrate of the drug transporters tested. In humans, mean maximum concentration of pudexacianinium in plasma was comparable across study groups regardless of renal impairment. Systemic exposure was highest with severe renal impairment and decreased in parallel with renal impairment severity. Geometric least-squares mean ratios for area under the plasma concentration–time curve from time 0 to time infinity were 1.53, 2.30, and 3.69, respectively, for mild, moderate, and severe renal impairment, versus matched participants with normal renal function. During the 48-h collection, 64% of pudexacianinium was recovered unchanged in urine in the severe renal impairment group versus ≥ 90% recovered in other groups. Mean renal clearance was comparable with estimated glomerular filtration rate of unbound drug. Pudexacianinium was well tolerated, with an acceptable safety profile.

Conclusion Pudexacianinium elimination occurs primarily through glomerular filtration. Renal impairment significantly affected pudexacianinium pharmacokinetics. Single intravenous doses of pudexacianinium were generally tolerable in all participants, regardless of renal impairment.

Trial registration.
ClinicalTrials.gov identifier: NCT05495581, registered August 9, 2022.

Keywords Pudexacianinium · ASP5354 · Pharmacokinetics · Renal elimination · Renal impairment · Glomerular filtration

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Introduction

Intraoperative ureteral injury (IUI) is an infrequent but significant complication of abdominopelvic surgery that can lead to serious complications, especially if left unrecognized and untreated [1]. Intraoperative identification of the ureters may be difficult, and abdominopelvic surgeries carry increased risk of IUI due to their close proximity to the ureters. Preoperative ureteral catheterization or stenting may be utilized in these high-risk, invasive procedures, but their effectiveness is controversial, and usage rates remain low [2, 3]. Intravenous (IV) and retrograde pyelography or urologic computed tomography can be utilized preoperatively to help avoid IUI, but these imaging techniques do not allow intraoperative ureteral identification [4, 5]. Image-guided surgery using near-infrared fluorescence (NIR-F) imaging is a promising technique that offers real-time visual information for surgeons and potentially reduces risk of IUI during surgery [6].

Methylene blue (MB) and indocyanine green (ICG) are two commercial products that can be used to aid ureteral identification during surgery, but neither are approved by the US Food and Drug Administration for this indication [6]. When MB is used as a fluorescent dye for NIR-F imaging, its excitation peak limits the depth of tissue penetration; therefore, MB is not optimal for ureteral identification [7]. As for indocyanine green, owing to its exclusive clearance by the liver, it can be used only with retrograde ureteral injection [8, 9]. Pudexacianinium chloride (ASP5354) is a novel imaging agent under clinical investigation for intraoperative anatomical visualization of ureters in adult and adolescent patients undergoing minimally invasive and open abdominopelvic surgery. It is an iodine-free chemical entity that exhibits unique hydrophilic properties through conjugation with cyclodextrin while retaining NIR-F characteristics. The chemical structure of pudexacianinium has been reported elsewhere [10]. Use of pudexacianinium has been assessed in nonclinical studies and subsequently in Phase 1 and Phase 2 clinical studies [10–12].

In a nonclinical study in minipigs, pudexacianinium was almost completely (95%) excreted into urine as the unchanged drug up to 6 h after administration [10]. In a Phase 1, double-blinded, randomized, placebo-controlled study (NCT03698305) conducted in healthy participants in the USA, manageable safety and tolerability profiles were demonstrated with single IV doses of pudexacianinium of up to 24 mg; urinary excretion was rapid and nearly complete, with almost all pudexacianinium (76.8–100%) excreted unchanged into urine [11]. Mean renal clearance (CL_R) was in the range of 3.57–4.92 L/h, which was nearly equivalent to the mean total clearance (CL; 4.38–6.01 L/h). No metabolites were found in plasma and urine samples (data on file). Similar pharmacokinetic (PK) and safety profiles were obtained in a Japanese Phase 1 study in healthy participants (NCT04878471) (data on file). Results from an analysis of covariance (ANCOVA) assessment of PK with the potential covariates of body weight, age, sex, and individual estimated glomerular filtration rate (eGFR) showed no significant difference in exposure (maximum plasma concentration [C_{max}] and area under the concentration–time curve [AUC]) between healthy American and Japanese participants (data on file).

A randomized, open-label, dose-ranging, Phase 2 study (NCT04238481) in adults undergoing laparoscopic colorectal surgery demonstrated that a single administration of pudexacianinium provides ureteral visualization for the full duration of minimally invasive, laparoscopic colorectal procedures at doses of 1 mg and 3 mg [12]; however, fluorescence intensity was stronger and more consistent at the 3 mg dose. Phase 3 studies (NCT05754333 and NCT05999747) using pudexacianinium 3 mg were completed in 2025.

Nonclinical and clinical data suggest that pudexacianinium is almost exclusively excreted unchanged into urine through the kidneys. Therefore, impaired renal function would likely impact both plasma and urine PK of pudexacianinium: compared with those without renal impairment, theoretically plasma concentration would be higher, urinary excretion would be lower, and urine concentration would be lower in participants with renal impairment. In general, renal clearance of drugs is determined by the combined effects of glomerular filtration and tubular secretion and reabsorption via renal drug transporters. Prior to the present study, the contribution of glomerular filtration and renal drug transporters to the CL_R of pudexacianinium had not been clear.

Owing to the exclusive excretion of pudexacianinium into the urine after IV administration, detection of excretory flow of pudexacianinium from the kidneys to the bladder using NIR-F imaging technology could facilitate ureter identification during surgery. In theory, ureter visualization would depend on the urine concentration of pudexacianinium in the ureter; therefore, real-time urine concentration of pudexacianinium is considered a good surrogate pharmacodynamic marker for visualization. Thus, if manageable safety and tolerability profiles are demonstrated in humans with renal impairment and sufficient urinary excretion is observed, surgical patients with renal impairment may be included as part of the target indication, given the prevalence of moderate to severe renal impairment of ~ 10% [13, 14]. In a nonclinical study using a rat model of renal impairment, in vivo ureteral imaging was successfully performed after pudexacianinium administration [15].

The objectives of the present study were to elucidate the mechanism of renal excretion of pudexacianinium and

to evaluate the effect of renal impairment on the PK of pudexacianinium. First, we conducted in vitro experiments using cells expressing major human renal drug transporters to investigate whether pudexacianinium is a substrate of these transporters. Subsequently, we conducted a dedicated renal impairment study in humans to assess the effect of renal impairment on the PK, safety, and tolerability of pudexacianinium.

Methods

In vitro study

To assess whether pudexacianinium is a substrate for efflux drug transporters, transcellular transport across pig kidney epithelial (LLC-PK1) cells expressing human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) was examined and compared with that across control cells. After the solution in either the apical side or the basal side was spiked with [^{14}C]pudexacianinium in the presence or absence of typical inhibitors, cells were incubated at 37 °C for 0.5, 1, and 2 h. After incubation, an aliquot was collected from the receiver side and radioactivity was measured using liquid scintillation counting. The permeated amount transported across cells was calculated from the radioactivity.

To assess whether pudexacianinium is a substrate for organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), organic cation transporter 2 (OCT2), multidrug and toxin extrusion 1 (MATE1), or multidrug and toxin extrusion 2-K (MATE2-K), transporter-mediated uptake of [^{14}C]pudexacianinium by human embryonic kidney 293 cells expressing human OAT1, OAT3, OCT2, MATE1, and MATE2-K was compared with that by control cells. Cells were incubated with [^{14}C]pudexacianinium in the presence or absence of typical inhibitors at 37 °C for 1, 2, 5, and 10 min. After incubation, cells were washed and lysed, and radioactivity of the cell lysate was measured using liquid scintillation counting. Cleared volumes were calculated from the radioactivity.

Details of the in vitro study methods are described in the Supplementary Information.

Clinical study

Study design

The study (NCT05495581) was a Phase 1 open-label, multicenter, single-dose, parallel-group study conducted at three sites in the USA and one site in Japan. A schematic of the study design is shown in Fig. S1. Renal impairment was expected to lead to clinically relevant increases in pudexacianinium exposure; therefore, a full PK study design was selected. Participants' individual estimated GFR (eGFR) values, calculated with equations shown below based on the Modification of Diet in Renal Disease (MDRD) formula and individual body surface area (BSA) [16, 17], were used for assignment to four groups (mild, moderate, and severe renal impairment and normal renal function):

$$eGFR\left(mL/min/1.73m^2 = 175 \times (standardized\ serum\ creatinine)^{-1.154} \times (age)^{-0.203} \times (0.742if\ female) \times (1.212if\ Black/African\ American)\right)$$

$$BSA\left(m^2\right) = 0.007184 \times weight(kg)^{0.425} \times height(cm)^{0.725}$$

$$Individual\ eGFR\,(mL/min) = eGFR\ \left(mL/min/1.73m^2\ by\ MDRD\right) \times BSA/1.73$$

An eGFR ≥ 90 mL/min was considered normal renal function, 60 to < 90 mL/min was considered mild renal impairment, 30 to < 60 mL/min was considered moderate renal impairment, and 15 to < 30 mL/min without requiring dialysis was considered severe renal impairment [18].

Healthy participants with normal renal function were enrolled to be demographically matched (1:1) by age (± 10 years), sex, and body mass index (BMI; ± 20%) to the participants in the mild, moderate, and severe renal impairment groups. One participant with normal renal function served as a matched control for multiple participants with renal impairment, as long as the renal impairment participants were in different impairment groups.

Eligible participants were admitted to a site on the day before dosing and received a single IV dose of pudexacianinium after an overnight fast of ≥ 10 h. Participants were allowed to consume water ad libitum throughout the study, including before and after pudexacianinium dosing. Participants remained on-site for 4 days/3 nights and returned for an end-of-study visit 5–9 days after the last sample collection.

All participants received a single dose of pudexacianinium 3 mg, which was the planned clinical dose. The dose was given as an IV bolus injection over approximately 10 s. The planned clinical dose is generally recommended as the appropriate dose to characterize PK of drugs in renal impairment studies [18]. Although renal impairment was expected to affect pudexacianinium PK, dose reduction was considered unnecessary in participants with renal impairment, given no change in C_{max} of the drug was anticipated with decreasing GFR owing to the IV bolus administration

and the manageable safety profile of pudexacianinium demonstrated up to a dose of 24 mg, as observed in the first-in-human Phase 1 study [11].

Study participants

Eligible participants were aged 18–75 years at screening for sites in the USA and 20–75 years at the time of consent for the site in Japan. A BMI in the range of 18.5–40.0 kg/m^2 and a body weight of > 50 kg at screening were required for sites in the USA, and a BMI in the range of 17.6–30.0 kg/m^2 and a body weight of > 50 kg for men and > 40 kg for women at screening were required for the site in Japan.

Participants with normal renal function were required to be in good health according to medical history, physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory tests, and to not have used any prescribed or nonprescribed drugs in the 2 weeks before pudexacianinium administration, except for occasional use of acetaminophen, topical dermatological products, hormonal contraceptives, and/or hormone replacement therapy. Participants with renal impairment were required to have stable renal impairment and to be without any clinically significant illness other than renal disease and conditions related to renal disease. Participants with a renal disease secondary to malignancy were excluded.

Participants who had received any moderate or strong inducers of cytochrome P450 3A in the 3 months before admission were excluded. In addition, participants were required to abstain from using inhibitors for transporters P-gp, BCRP, OAT1, OAT3, MATE1, and MATE2-K during the study. Participants with renal impairment were allowed to use concomitant medication for their underlying condition, but a change in dose regimen of medically required medication during the study was not allowed, except for minor dose changes that were agreed upon between the investigator and sponsor.

Pharmacokinetics

Blood samples for plasma PK were collected before dosing on Day 1 and at 5, 15, 30, 45, and 60 min and 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h after dosing on Day 1. Urine samples were collected before dosing on Day 1 and at intervals 0–2, 2–4, 4–8, 8–12, 12–24, 24–36, and 36–48 h after dosing on Day 1.

Plasma and urine concentrations were measured at CMIC Pharma Science Co., Ltd (Hyogo, Japan) using validated high-performance liquid chromatography–tandem mass spectrometry assays as previously described [11]. In brief, for plasma and urine assays, sample purification used Oasis HLB µElution solid-phase extraction plates (Waters™, Milford, MA, USA). Chromatographic separation utilized a CAPCELL PAK ADME 2 µm, 2.1 × 20 mm column (Osaka Soda Co., Ltd, Osaka, Japan) at 60 °C. The elution profile was a gradient of acetonitrile and water containing formic acid. A QTRAP 6500 mass spectrometer (Sciex, Framingham, MA, USA) with TurboIonSpray source in positive ion mode was used to perform multiple reaction monitoring of the mass transitions 1015 → 325 m/z (pudexacianinium) and 1019 → 717 m/z (internal standard). The lower limit of quantification was defined as 1.00 ng/mL for plasma concentrations and 20.0 ng/mL for urine concentrations. All samples were analyzed within established stabilities. Inter-assay precision was ≤ 10.6% for plasma and ≤ 14.1% for urine. Inter-assay accuracy (percentage relative error) ranged from − 2.5% to 3.5% for plasma and from 2.0% to 0.0% for urine.

The following PK parameters were calculated by noncompartmental analysis using Phoenix WinNonlin software, version 8.3 (Certara, Princeton, NJ, USA): C_{max}; AUC from time 0 to time infinity (AUC_{inf}); AUC from time 0 to time of last measurable concentration (AUC_{last}); CL; volume of distribution during the terminal elimination phase; amount of administered dose excreted (Ae) from time 0 to time infinity (Ae_{inf}); Ae from time 0 to time of last measurable concentration (Ae_{last}); percentage of Ae_{inf}; percentage of Ae_{last}; and renal clearance (CL_R).

Protein binding

To assess the protein binding of pudexacianinium, blood samples were collected on Day 1 at 5 min, 1 h, and 8 h after dosing. Pudexacianinium plasma protein binding was determined using a validated liquid chromatography–high resolution mass spectrometry method. Unbound (free) and total concentrations of pudexacianinium in each sample were measured in ultrafiltrate and plasma, respectively, at CMIC Pharma Science Co., Ltd. Ultrafiltrate was prepared from human plasma using an Amicon Ultra 10 kDa centrifugal filter (Merck, Darmstadt, Germany). Ultrafiltrate and plasma samples were measured in a single assay using a 0.125 mL aliquot of ultrafiltrate and plasma (4:1, v/v) and a stable isotope-labeled internal standard (d_{12}-pudexacianinium). The ultrafiltrate concentration range was 0.500–250 ng/mL, and the plasma concentration range was 2.00–1000 ng/mL. Sample purification used Oasis HLB µElution solid-phase extraction plates (Waters, Milford, MA, USA). Chromatographic separation utilized an ACQUITY UPLC CSH C18 1.7 µm, 2.1 × 50 mm column (Waters, Milford, MA, USA) at 70 °C. The elution profile was a gradient of acetonitrile and water containing ammonium formate at 5 mmol/L. An Orbitrap Exploris™ 120 mass spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) was used to monitor the + 2

ions 1522.0986 m/z (pudexacianinium) and 1528.1362 (internal standard). Inter-assay precision was ≤ 6.9% for plasma and ≤ 7.5% for ultrafiltrate. Inter-assay accuracy (percentage relative error) was in the ranges 1.0–5.4% for plasma and 0.1–5.9% for ultrafiltrate.

For each sample, the fraction unbound (f_u) was calculated as the ultrafiltrate concentration divided by the plasma concentration. For each participant, the f_u was calculated as the geometric mean of 3 time points.

Safety and tolerability

Safety and tolerability were assessed in all participants; this included assessment of vital signs, physical examinations, 12-lead ECGs, and clinical laboratory tests. Adverse events (AEs), including abnormal clinical laboratory values, were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 6.0 and categorized by organ class and preferred term using the Medical Dictionary for Regulatory Activities, version 26.0. Green coloration of urine was an expected reversible effect that has been observed in previous clinical studies of pudexacianinium [11] and does not lead to any untoward clinical symptoms. Therefore, green coloration of urine was not considered an AE; however, it was assessed, and its incidence was recorded. Urine samples collected after pudexacianinium dosing were visually inspected by clinical site staff and documented for incidence of green coloration. When it occurred, the coloration was assessed at every urination until it resolved. The start and stop dates and times were recorded for participants who experienced green coloration of urine.

Statistical analyses

A planned sample size of up to 36 participants (6 participants per renal impairment group and up to 18 participants for the normal renal function-to-match group) was determined based on a precedent set by other PK studies of similar nature.

Data manipulation, summary statistics, and statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Baseline demographic and other characteristics, vital signs, clinical laboratory findings, 12-lead ECG results, and treatment-emergent AEs (TEAEs) were summarized for the safety analysis set, which consisted of all participants who received the study drug. Plasma and urine PK were summarized for the PK analysis set, which consisted of participants who received the study drug and for whom concentration data were available to facilitate derivation of at least one primary PK parameter.

To evaluate the effect of renal impairment on pudexacianinium PK, a separate ANCOVA for each renal impairment group (mild, moderate, and severe) was performed on natural logarithmic-transformed PK parameters (AUC_{inf}, AUC_{last}, and C_{max}) with renal function group as a fixed effect and age, sex, and BMI as candidate covariates. Within the ANCOVA, the least-squares (LS) mean differences between the renal impairment group and the normal-to-match group, along with 90% confidence intervals for the differences, were estimated. Geometric LS mean ratios and their corresponding 90% confidence intervals were presented for each PK parameter against the normal-to-match group. A linear regression for the relationship between individual eGFR and CL or CL_R of pudexacianinium was performed, and a graphical assessment of the association was produced.

Results

In vitro study

The radiochemical purity of [^{14}C]pudexacianinium was ≥ 93.4% throughout the study.

Transcellular transport of [^{14}C]pudexacianinium in control, P-gp-expressing and BCRP-expressing cells were examined (Fig. S2). Corrected apparent permeability coefficient ratio (CP_R) values of [^{14}C]pudexacianinium at 1 µmol/L and 10 µmol/L, respectively, were 0.7 and 1.4 for P-gp and 0.8 and 1.3 for BCRP. In the presence of the typical inhibitors (verapamil for P-gp and Ko143 for BCRP), CP_R values of pudexacianinium at 1 µmol/L and 10 µmol/L, respectively, were 1.2 and 1.1 for P-gp and 0.8 and 1.2 for BCRP.

The cleared volumes of [^{14}C]pudexacianinium at 1 µmol/L and 10 µmol/L into cells expressing OAT1, OAT3, OCT2, MATE1, and MATE2-K were comparable with those into control cells (Fig. S3).

Demographics for participants in the clinical study

In total, 28 participants were enrolled in the study and received pudexacianinium. There were 6 participants each in the mild, moderate, and severe renal impairment groups and 10 participants with normal renal function. All participants completed the study adhering to the protocol and were included in the safety analysis set. Baseline characteristics and demographics were generally balanced across the groups (Table 1). The age of enrolled participants ranged from 51 to 75 years. The BMI of enrolled participants was in the range of 21.66–38.02 kg/m^2. The majority of the participants were White (71.4%).

Table 1 Participant demographics and baseline characteristics

Characteristic	Mild ($n=6$)	Normal-to-match mild impairment ($n=6$)[a]	Moderate ($n=6$)	Normal-to-match moderate impairment ($n=6$)[a]	Severe ($n=6$)	Normal-to-match severe impairment ($n=6$)[a]	Normal total ($n=10$)	Total ($N=28$)
Male sex, *n* (%)	3 (50.0)	3 (50.0)	2 (33.3)	2 (33.3)	4 (66.7)	4 (66.7)	5 (50.0)	14 (50.0)
Hispanic or Latino ethnicity, n (%)	2 (33.3)	1 (16.7)	3 (50.0)	1 (16.7)	2 (33.3)	3 (50.0)	3 (30.0)	10 (35.7)
Race, *n* (%)	4 (66.7)	4 (66.7)	5 (83.3)	4 (66.7)	4 (66.7)	4 (66.7)	7 (70.0)	20 (71.4)
White	2 (33.3)	0 (0)	1 (16.7)	0 (0)	1 (16.7)	0 (0)	0 (0)	4 (14.3)
Black/African American	0 (0)	2 (33.3)	0 (0)	2 (33.3)	1 (16.7)	2 (33.3)	3 (30.0)	4 (14.3)
Asian								
Age (years), mean (SD)	63.7 (5.7)	60.5 (6.4)	62.5 (10.0)	61.5 (7.0)	61.7 (8.9)	59.0 (5.8)	61.3 (6.2)	62.1 (7.3)
BMI (kg/m^2), mean (SD)	29.99 (5.17)	27.61 (4.21)	28.42 (5.73)	27.74 (1.99)	30.88 (4.92)	28.44 (2.75)	28.24 (3.31)	29.22 (4.52)

[a]Some participants with normal renal function served as matched controls for multiple participants with renal impairment

BMI body mass index, *SD* standard deviation

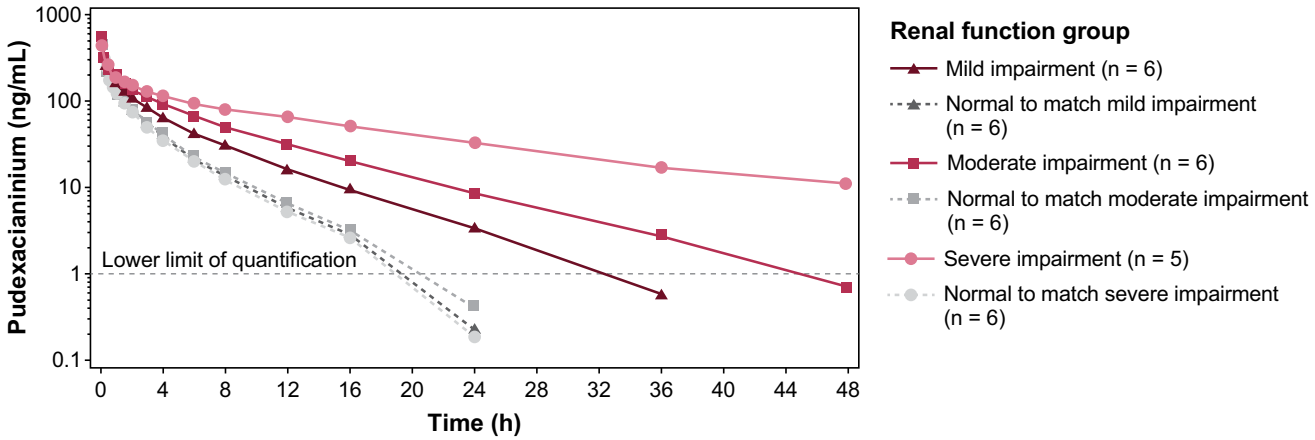

Fig. 1 Mean plasma concentration–time profiles for pudexacianinium by renal function group. Data are shown on a semi-logarithmic scale. Some participants with normal renal function served as matched controls for multiple participants with renal impairment

Pharmacokinetics

One participant in the severe renal impairment group was excluded from the PK analysis set, because based on the observed PK profile, it was suspected that pudexacianinium was administered extravascularly and not intravascularly (Fig. S4). This participant showed unusually low plasma concentrations during the first 2 h after administration (Fig. S4b) but showed comparable plasma concentrations to others thereafter (Fig. S4a). Although extravascular administration was suspected in this participant, overall plasma and urine concentrations were not notably different from others.

C_{max} was observed at the first sampling time point after dosing of pudexacianinium in all but two participants, for whom it was observed at the second post-dose sampling time point. Pudexacianinium elimination slowed with increasing severity of renal impairment (Fig. 1).

Mean plasma C_{max} values were comparable between the renal impairment groups and their respective normal-to-match groups, whereas higher variability was observed in the renal impairment groups compared with the normal-to-match groups (Table 2). The AUC_{last}, AUC_{inf}, and terminal elimination half-life ($t_{½}$) increased with increasing degree of renal impairment, with an accompanying decrease in CL. The geometric LS mean ratios of the AUC_{inf} were 1.53, 2.30, and 3.69 in the mild renal impairment, moderate renal impairment, and severe renal impairment groups, respectively, versus matched normal renal function groups. The change in $t_{½}$ was of a similar magnitude to the change in CL: approximately 1.5-fold for participants with mild renal impairment, approximately 1.8-fold for participants with moderate renal impairment, and approximately 4.0-fold for participants with severe renal impairment compared with their respective normal-to-match groups.

Plasma protein binding for pudexacianinium was independent of time and concentration for all renal function groups. Average f_u in plasma (geometric mean of 3 time points) was approximately 0.8 across pudexacianinium

Table 2 Plasma pharmacokinetic parameters of pudexacianinium by renal function group

Category/statistic		Mild ($n=6$)	Normal-to-match mild impairment ($n=6$)[a]	Moderate ($n=6$)	Normal-to-match moderate impairment ($n=6$)[a]	Severe ($n=5$)[b]	Normal-to-match severe impairment ($n=6$)[a]	Normal total ($n=10$)
C_{max}, µg/mL	Mean (SD)	0.476 (0.250)	0.446 (0.0688)	0.535 (0.254)	0.435 (0.0788)	0.428 (0.120)	0.437 (0.0772)	0.422 (0.0629)
	% CV	52.5	15.4	47.4	18.1	28.0	17.7	14.9
	GMR	0.971		1.14		1.01		–
	90% CI	(0.660, 1.43)		(0.778, 1.66)		(0.818, 1.24)		
$t_{max,}$ h	Median	0.108	0.0830	0.0830	0.0830	0.0830	0.0830	0.0830
	Min, max	0.0500, 0.250	0.0670, 0.0830	0.0830, 0.250	0.0670, 0.100	0.0830, 0.133	0.0670, 0.0830	0.0670, 0.100
AUC_{last}, h·µg/mL	Mean (SD)	0.944 (0.0792)	0.588 (0.0900)	1.41 (0.535)	0.603 (0.130)	2.38 (1.09)	0.554 (0.0817)	0.597 (0.105)
	% CV	8.4	15.3	38.0	21.6	45.7	14.7	17.6
	GMR	1.53		2.31		3.49		–
	90% CI	(1.39, 1.68)		(1.90, 2.80)		(2.01, 6.07)		
AUC_{inf}, h·µg/mL	Mean (SD)	0.957 (0.0790)	0.599 (0.0885)	1.43 (0.545)	0.613 (0.129)	2.64 (1.20)	0.565 (0.0817)	0.607 (0.104)
	% CV	8.2	14.8	38.2	21.1	45.6	14.5	17.1
	GMR	1.53		2.30		3.69		–
	90% CI	(1.39, 1.67)		(1.90, 2.79)		(2.09, 6.53)		
$t_{½}$, h	Mean (SD)	5.36 (0.783)	3.57 (0.227)	6.52 (1.55)	3.54 (0.404)	14.3 (4.07)	3.54 (0.469)	3.58 (0.410)
	% CV	14.6	6.4	23.7	11.4	28.5	13.3	11.4
CL, L/h	Mean (SD)	3.15 (0.245)	5.08 (0.638)	2.29 (0.622)	5.09 (1.13)	1.67 (1.54)	5.41 (0.859)	5.08 (0.900)
	% CV	7.8	12.6	27.1	22.2	92.1	15.9	17.7
V_z, L	Mean (SD)	24.2 (2.92)	26.1 (2.77)	21.0 (6.46)	25.6 (4.01)	34.2 (32.4)	27.3 (3.23)	26.0 (3.34)
	% CV	12.0	10.6	30.8	15.7	94.7	11.8	12.9
f_u	Mean (SD)	0.785 (0.0467)	0.790 (0.0629)	0.767 (0.0614)	0.793 (0.0669)	0.754 (0.0918)	0.763 (0.0478)	0.789 (0.0521)
	% CV	6.0	8.0	8.0	8.4	12.2	6.3	6.6

Plasma pharmacokinetic parameters were estimated using Phoenix WinNonlin, version 8.3

[a]Some participants with normal renal function served as matched controls for multiple participants with renal impairment

[b]One participant with severe renal impairment and suspected extravascular administration was excluded from the pharmacokinetic analysis set

% *CV* percent coefficient of variation, *AUC* area under the concentration–time curve, AUC_{inf} AUC from time 0 to time infinity, AUC_{last} AUC from time 0 to time of last measurable concentration, *CI* confidence interval, *CL* total clearance, C_{max} maximum concentration, f_u fraction unbound, *GMR* geometric least-squares mean ratio, *h*, hours, *max* maximum, *min* minimum, *SD* standard deviation, $t_{½}$ terminal elimination half-life, t_{max} time of maximum concentration, V_z volume of distribution during the terminal elimination phase

concentrations and renal function groups: normal renal function (total), 0.789; mild impairment, 0.785; moderate impairment, 0.767; and severe impairment, 0.754.

Renal excretion of pudexacianinium slowed with increasing severity of renal impairment (Fig. 2). One participant in the severe renal impairment group had much lower urine concentrations than the other participants in the same group, resulting in a large standard deviation. In the first 4 h after dosing, 67.4%, 42.3%, 41.1%, and 11.4% of the administered dose was excreted into urine as the unchanged drug in the normal renal function (total), mild impairment, moderate impairment, and severe impairment groups, respectively. Over the 24-h period following dosing, 91.8%, 87.3%, 93.2%, and 48.0% of the administered dose was excreted into urine as the unchanged drug in the normal (total), mild impairment, moderate impairment, and severe impairment groups, respectively. Except for in the severe renal impairment group, the majority of the administered dose was excreted into urine within 24 h. Over the 48-h collection interval, 64% of the administered dose was recovered as unchanged drug in urine in the severe renal impairment group, whereas approximately 90% or more was recovered in urine in the other renal function groups (Table 3). The mean CL_R was nearly equivalent to the mean CL in all renal function groups except for the severe renal impairment group, driven largely by data from one participant in the group who had very low CL_R. CL and CL_R increased proportionally and were correlated with increasing individual eGFR ($R^2=0.6543$ and 0.7326, respectively; Fig. 3).

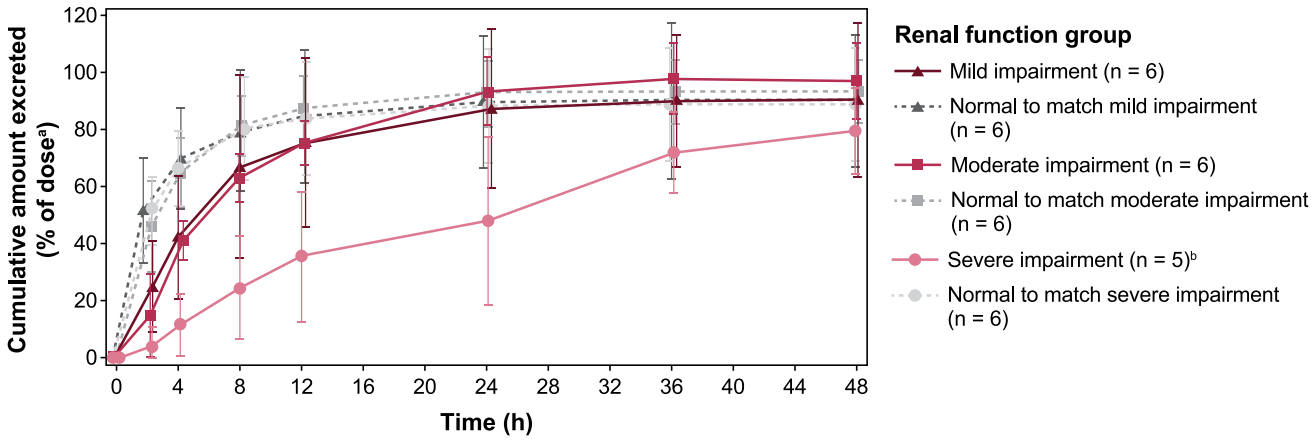

Fig. 2 Mean cumulative proportion of pudexacianinium dose excreted into urine as unchanged drug by renal function group. Some participants with normal renal function served as matched control for multiple participants with renal impairment. [a]Error bars represent standard deviation. [b]Urine samples were available for 55 participants for up to 24 h, but after that $n=4$, as one participant's urine sample was lost during the 24–36-h collection. h, hours

Table 3 Urine pharmacokinetic parameters of pudexacianinium by renal function group

Category/statistic		Mild ($n=6$)	Normal-to-match mild impairment ($n=6$)[a]	Moderate ($n=6$)	Normal-to-match moderate impairment ($n=6$)[a]	Severe ($n=5$)[b]	Normal-to-match severe impairment ($n=6$)[a]	Normal total ($n=10$)
Ae_{inf} (mg)	Mean (SD)	2.70 (0.809)	2.69 (0.736)	2.98 (0.395)	2.80 (0.350)	2.15 (1.25)	2.65 (0.634)	2.76 (0.576)
	% CV	30.0	27.3	13.2	12.5	58.1	24.0	20.9
Ae_{last} (mg)	Mean (SD)	2.71 (0.813)	2.70 (0.696)	2.96 (0.376)	2.80 (0.334)	1.92 (1.11)	2.67 (0.598)	2.77 (0.546)
	% CV	30.0	25.7	12.7	11.9	57.8	22.4	19.7
$Ae_{inf\%}$ (%)	Mean (SD)	90.1 (27.0)	89.8 (24.5)	99.5 (13.2)	93.3 (11.7)	71.5 (41.5)	88.3 (21.1)	92.0 (19.2)
	% CV	30.0	27.3	13.2	12.5	58.1	24.0	20.9
$Ae_{last\%}$ (%)	Mean (SD)	90.4 (27.1)	90.1 (23.2)	98.7 (12.5)	93.4 (11.1)	64.0 (37.0)	88.9 (19.9)	92.3 (18.2)
	% CV	30.0	25.7	12.7	11.9	57.8	22.4	19.7
CL_R (L/h)	Mean (SD)	2.87 (0.960)	4.55 (1.40)	2.28 (0.700)	4.72 (1.09)	0.716 (0.386)	4.74 (1.22)	4.65 (1.24)
	% CV	33.5	30.9	30.8	23.0	53.9	25.6	26.7

Urine pharmacokinetic parameters were calculated using Phoenix WinNonlin, version 8.3

[a]Some participants with normal renal function served as matched controls for multiple participants with renal impairment

[b]One participant with severe renal impairment and suspected extravascular administration was excluded from the pharmacokinetic analysis set

%CV percent coefficient of variation, *Ae* amount of administered dose excreted, Ae_{inf} Ae from time 0 extrapolated to time infinity, $Ae_{inf\%}$ percentage of Ae_{inf};

Ae_{last} Ae from time 0 to last measurable concentration, $Ae_{last\%}$ percentage of Ae_{last}, CL_R renal clearance, *SD* standard deviation

Safety and tolerability

No deaths, serious AEs, or TEAEs leading to the withdrawal of treatment were reported in this study. All enrolled participants completed the study up to the end-of-study visit. Overall, five participants (17.9%) experienced a total of seven TEAEs. Of these TEAEs, only headache and hyperbilirubinemia were considered by the investigator to be drug related. All TEAEs were considered mild in severity, except for the events of abdominal distension and flatulence reported for one participant in the moderate renal impairment group and considered by the investigator to be moderate in severity. There were no other clinical laboratory (hematology, biochemistry, and urinalysis) results, vital signs, or routine 12-lead ECG measurements reported as TEAEs in this study.

Green coloration of urine was observed in 12 participants (43%): 5 (50%) in the normal renal function group; and 3 (50%), 3 (50%), and 1 (17%), respectively, in the mild renal impairment, moderate renal impairment, and severe renal impairment groups. Mean duration of having green coloration of urine was 4.0 h in the normal renal function group and 6.1, 7.6, and 15.9 h respectively, in the mild renal impairment, moderate renal impairment, and severe renal impairment groups.

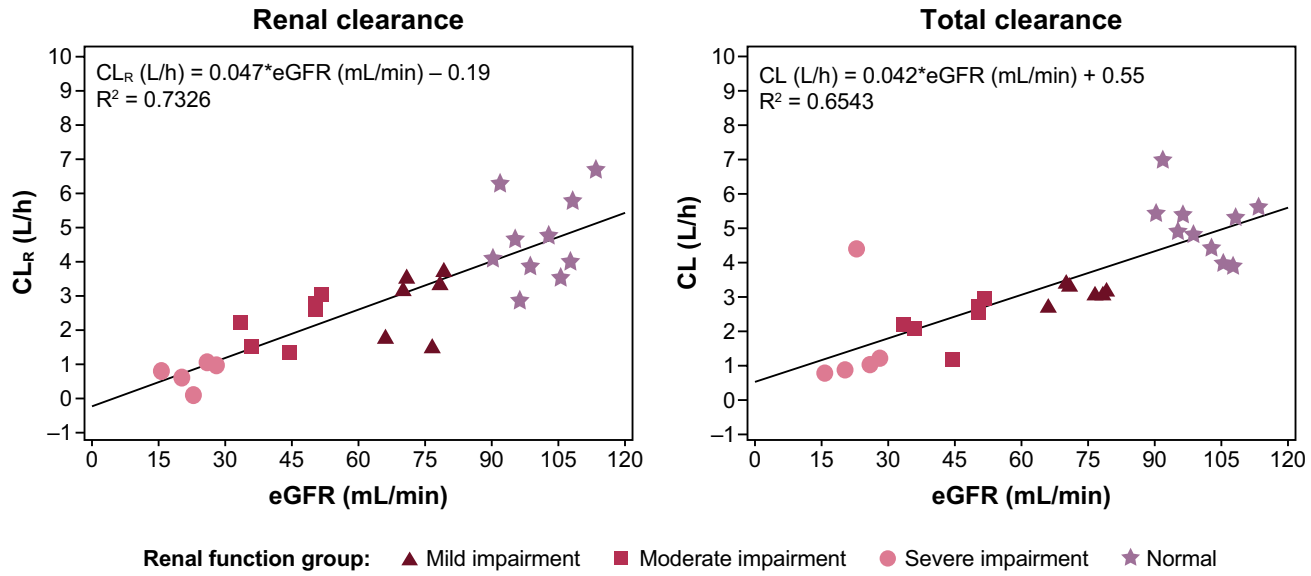

Fig. 3 Relationship between eGFR and CL_R and CL of pudexacianinium. Linear regression analyses were conducted for eGFR versus CL_R and for eGFR versus CL. CL, total clearance; CL_R, renal clearance; eGFR, estimated glomerular filtration rate; h, hours

Discussion

The present study comprised two parts: an in vitro transporter study and a Phase 1 clinical study in participants with renal impairment or normal renal function. The clinical study evaluated the effect of renal impairment on the PK, safety, and tolerability of pudexacianinium, and, together with the in vitro study, led to the elucidation of the elimination pathway for pudexacianinium.

Results of the in vitro experiments suggest that pudexacianinium is not a substrate of any of the major human renal drug transporters, P-gp, BCRP, OAT1, OAT3, OCT2, MATE1, and MATE2-K, and that renal drug transporters do not contribute to the elimination of pudexacianinium. Results of the Phase 1 study demonstrated that, as expected, renal impairment markedly affects pudexacianinium PK, with apparent increases in plasma exposure and slower excretion into urine in participants with renal impairment compared with in healthy participants with normal renal function. As expected for intravenously administered drugs, mean plasma C_{max} values were comparable between renal impairment and matched normal groups. The underlying cause of the higher variability of C_{max} in the renal impairment groups than in the healthy participants is not clear. The variability of C_{max} was highest in participants with mild renal impairment and next highest in those with moderate and severe renal impairment; no clear correlation was found that could suggest that variability increases with severity of renal impairment. Moreover, previous reports of renal impairment studies do not consistently show that the variability of C_{max} or other PK parameters such as AUC is higher in participants with renal impairment than in healthy participants after IV administration over a short period of time [19, 20]. The mean CL_R was generally equivalent to the mean CL, indicating that elimination of pudexacianinium mostly occurs via renal excretion. Plasma protein binding was independent of time and concentration regardless of severity of renal impairment (f_u, approximately 0.8). Using mean f_u values for each renal function category, $f_u \times$ mean eGFR for each category would be 4.78, 3.46, 2.04, and 0.76 L/h, respectively, for the normal renal function, mild renal impairment, moderate renal impairment, and severe renal impairment groups. These values match the mean CL_R for each renal function category: 4.65 L/h for the normal function group and 2.87, 2.28, and 0.72 L/h, respectively, for the mild renal impairment, moderate renal impairment, and severe renal impairment groups. This, added to the strong correlation between CL_R and eGFR (see Fig. 3) and the absence of any renal drug transporters contributing to renal excretion as suggested from the in vitro study, indicates that, more specifically, elimination of pudexacianinium can be explained almost entirely by glomerular filtration.

Zhang et al. have summarized reports of five drugs (telbivudine, entecavir, varenicline, emtricitabine, and lomefloxacin) that are mainly cleared by the renal route and compared the extent of exposure increase of these drugs in patients with severe renal impairment with that in individuals with normal renal function [21]. For entecavir, varenicline, emtricitabine, and lomefloxacin, tubular secretion via renal transporters was reported or suggested to contribute to their renal excretion [22–25]. For telbivudine, results from a renal impairment study suggested that it is mainly cleared via glomerular filtration, and notably, that the reported

increase in exposure of this drug (3.4-fold) is similar to that of pudexacianinium (3.69-fold) [26].

In terms of safety data, single IV doses of pudexacianinium 3 mg were well tolerated, with mostly mild AEs reported. Severity of renal impairment did not appear to affect the incidence or severity of AEs. Green coloration of urine was also assessed, because this was an expected event with pudexacianinium that does not lead to any untoward clinical symptoms. The incidence of green coloration was lower in the severe renal impairment group than in any of the other groups; however, duration of this coloration increased as renal impairment worsened. Although the determination of "green urine" will inherently vary by assessor, these data can be explained by the PK characteristics of pudexacianinium. The renal excretion rate and initial urine concentration of pudexacianinium decreases with increasing severity of renal impairment, which explains the low incidence of green coloration of urine in the severe renal impairment group. In addition, when green coloration of urine is observed after administration, the duration of this coloration will be longer with increasing severity of renal impairment owing to the slower decrease in urine concentration.

The present study has several limitations. First, there may be a possibility of other lesser-known renal drug transporters contributing to either tubular secretion or reabsorption of pudexacianinium in the kidney. However, CL_R being comparable to $f_u \times GFR$ in both the clinical study and the in vitro study should adequately indicate the absence of transporters that substantially contribute to the elimination of pudexacianinium. Second, there was one participant in the severe renal impairment group with unreasonably low plasma and urine concentrations throughout the sampling period, compared with those of other participants with severe renal impairment (Figs. S4 and S5). Surprisingly, green coloration of urine was observed for approximately 16 h in this participant. An exploratory metabolite profiling study using plasma and urine samples from this participant was conducted, but no metabolites were observed (data on file). However, despite these investigations, mechanisms that could explain the observed low concentrations for this participant have not been identified. When excluding this participant, the mean CL_R was nearly equivalent to the mean CL in all renal function groups, and the mean percentage of Ae_{last} for severe renal impairment was approximately 80%. Last, as with most Phase 1 studies, the clinical study was conducted in a relatively small population.

In this study, acceptable safety and tolerability profiles were demonstrated in participants with renal impairment, and sufficient urinary excretion of pudexacianinium was observed. The in vitro study and the clinical study together suggest that the majority of pudexacianinium elimination is through glomerular filtration. The safety profile and urinary excretion of pudexacianinium suggest that efficacy (ureter visualization) may be achievable in the renal impairment population without dose adjustment, indicating the potential for their inclusion as target patients. A single IV dose of pudexacianinium 3 mg was selected for the Phase 3 clinical program to provide optimal conspicuity for the ureter for the duration of the surgery in all intended participants, including those with severe renal impairment having an individual eGFR ≥ 15 mL/min. The safety profile as well as the clinical utility of pudexacianinium in this population will be further evaluated in the Phase 3 studies.

Conclusion

Results from in vitro transporter experiments suggest that pudexacianinium is not a substrate of the major renal drug transporters tested. Renal impairment significantly increased pudexacianinium exposure in human participants. The in vitro and Phase 1 studies suggest that the majority of pudexacianinium elimination is through glomerular filtration. Pudexacianinium had acceptable safety and tolerability profiles in participants with moderate or severe renal impairment, and sufficient urinary excretion of pudexacianinium was observed in these participants, suggesting the potential clinical utility of pudexacianinium for this population.

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Author contributions Study design: TK, ST, GPH, TW, MS, TM, and AK; Conduct and acquisition of data: NS, MN, MM, TM, KSC, JMN, ALF, and HS; Analysis of study data: TK, ST, GPH, TW, MS, SG, NM, MN, MM, and TM; Interpretation of study data: TK, ST, GPH, TW, MS, SG, and AK; Writing of the manuscript: All authors.

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Data availability Details for how researchers may request access to anonymized participant level data, trial level data and protocols from Astellas sponsored clinical trials can be found at [https://www.clinicaltrials.astellas.com/transparency/](https://url.uk.m.mimecastprotect.com/s/2yWyCDqYATB5K2XCWfQIjCk1F?domain=clinicaltrials.astellas.com).

Declarations

Ethical approval and consent to participate The clinical study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice, and the International Council for Har-

monisation of Technical Requirements for Pharmaceuticals for Human Use guidelines. The protocol, its amendments, informed consent forms, investigator's brochure, and other relevant documents (e.g., advertisements) were reviewed and approved by the Institutional Review Board of the participating sites (Advarra, Inc., Columbia, MD, for sites in the USA; and Medical Corporation Houeikai, Toshima-ku, Tokyo, for the site in Japan) before the study was initiated. All participants provided written informed consent before participation in the study.

Competing interests TK, MS, TM, MN, SG, AK, MM, and ST are employees of Astellas Pharma Inc. NS is an employee of Astellas Research Institute of America, LLC. TW and GPH are employees of Astellas Pharma Global Development, Inc. KSC, JMN, ALF, and HS have no conflicts of interest to declare.

References

1. Abboudi H, Ahmed K, Royle J, Khan MS, Dasgupta P, N'Dow J (2013) Ureteric injury: a challenging condition to diagnose and manage. Nat Rev Urol 10(2):108–115. https://doi.org/10.1038/nrurol.2012.254
2. Burks FN, Santucci RA (2014) Management of iatrogenic ureteral injury. Ther Adv Urol 6(3):115–124. https://doi.org/10.1177/1756287214526767
3. Teeluckdharry B, Gilmour D, Flowerdew G (2015) Urinary tract injury at benign gynecologic surgery and the role of cystoscopy. Obstet Gynecol 126(6):1161–1169. https://doi.org/10.1097/aog.0000000000001096
4. Brandes S, Coburn M, Armenakas N, McAninch J (2004) Diagnosis and management of ureteric injury: an evidence-based analysis. BJU Int 94(3):277–289. https://doi.org/10.1111/j.1464-410x.2004.04978.x
5. Ahn CB, Kim JH, Park GK, Park KY, Bao K, Lee JW et al (2019) Prognostic imaging of iatrogenic and traumatic ureteral injury by near-infrared fluorescence. Quant Imaging Med Surg 9(6):1056–1065. https://doi.org/10.21037/qims.2019.06.15
6. Slooter MD, Janssen A, Bemelman WA, Tanis PJ, Hompes R (2019) Currently available and experimental dyes for intraoperative near-infrared fluorescence imaging of the ureters: a systematic review. Tech Coloproctology 23(4):305–313. https://doi.org/10.1007/s10151-019-01973-4
7. Verbeek FPR, Van DVJR, Schaafsma BE, Swijnenburg R, Gaarenstroom KN, Elzevier HW et al (2013) Intraoperative near infrared fluorescence guided identification of the ureters using low dose methylene blue: A first in human experience. J Urol 190(2):574–579. https://doi.org/10.1016/j.juro.2013.02.3187
8. Lee Z, Moore B, Giusto L, Eun DD (2015) Use of indocyanine green during robot-assisted ureteral reconstructions. Eur Urol 67(2):291–298. https://doi.org/10.1016/j.eururo.2014.08.057
9. Siddighi S, Yune JJ, Hardesty J (2014) Indocyanine green for intraoperative localization of ureter. Am J Obstet Gynecol 211(4):436.e1-436.e2. https://doi.org/10.1016/j.ajog.2014.05.017
10. Fushiki H, Yoshikawa T, Matsuda T, Sato T, Suwa A (2023) Preclinical development and validation of ASP5354: A near-infrared fluorescent agent for intraoperative ureter visualization. Mol Imaging Biol 25(1):74–84. https://doi.org/10.1007/s11307-021-01613-0
11. Murase T, Takizawa M, Galitz L, Flach S, Murray V, Gufford B et al (2021) Randomized, double-blind, controlled study to evaluate safety and pharmacokinetics of single ascending doses of ASP5354, an investigational imaging product, in healthy adult volunteers. Clin Pharmacol Drug Dev 10(12):1460–1468. https://doi.org/10.1002/cpdd.1013
12. Albert M, Delgado-Herrera L, Paruch J, Gerritsen-van Schieveen P, Kishimoto T, Takusagawa S et al (2023) Pudexacianinium (ASP5354) chloride for ureter visualization in participants undergoing laparoscopic, minimally invasive colorectal surgery. Surg Endosc 37(9):7336–7347. https://doi.org/10.1007/s00464-023-10193-9
13. Kovesdy CP (2022) Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl 12(1):7–11. https://doi.org/10.1016/j.kisu.2021.11.003
14. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS et al (2016) Global prevalence of chronic kidney disease - A systematic review and meta-analysis. PLoS ONE 11(7):e01587. https://doi.org/10.1371/journal.pone.0158765
15. Teranishi K (2023) Evaluation of the utilization of near-infrared fluorescent contrast agent ASP5354 for in vivo ureteral identification in renal diseases using rat models of gentamicin-induced acute kidney injury. Diagnostics 13(10):1823. https://doi.org/10.3390/diagnostics13101823
16. Levey AS, Coresh J, Greene T, Stevens LA, Zhang Y, Hendriksen S et al (2006) Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 145(4):247–254. https://doi.org/10.7326/0003-4819-145-4-200608150-00004
17. Du Bois D, Du Bois EF (1989) A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition 5:303–311. Discussion 312–303
18. FDA Guidance for Industry (2020) Pharmacokinetics in patients with impaired renal function: Study design, data analysis, and impact on dosing and labeling. https://www.fda.gov/media/78573/download. Accessed 22 Jan 2025
19. Pöschel KA, Bucha E, Esslinger HU, Nörtersheuser P, Jansa U, Schindler U, Nowak G et al (2000) Pharmacodynamics and pharmacokinetics of polyethylene glycol-hirudin in patients with chronic renal failure. Kidney Int 58(6):2478–2484. https://doi.org/10.1046/j.1523-1755.2000.00431.x
20. Nafziger AN, Arscott KA, Cochrane K, Skobieranda F, Burt DA, Fossler MJ (2020) The influence of renal or hepatic impairment on the pharmacokinetics, safety, and tolerability of oliceridine. Clin Pharmacol Drug Dev 9(5):639–650. https://doi.org/10.1002/cpdd.750
21. Zhang L, Xu N, Xiao S, Arya V, Zhao P, Lesko LJ et al (2012) Regulatory perspectives on designing pharmacokinetic studies and optimizing labeling recommendations for patients with chronic kidney disease. J Clin Pharmacol 52(S1):79S-90S. https://doi.org/10.1177/0091270011415410
22 Faessel HM, Obach RS, Rollema H, Ravva P, Williams KE, Burstein (2010) A review of the clinical pharmacokinetics and pharmacodynamics of varenicline for smoking cessation. Clin

Pharmacokinet. 49(12):799–816. https://doi.org/10.2165/11537850-000000000-00000
23. Nakatani-Freshwater T, Taft DR (2008) Renal excretion of emtricitabine I: Effects of organic anion, organic cation, and nucleoside transport inhibitors on emtricitabine excretion. J Pharm Sci 97(12):5401–5410. https://doi.org/10.1002/jps.21370
24. Blum RA, Schultz RW, Schentag JJ (1990) Pharmacokinetics of lomefloxacin in renally compromised patients. Antimicrob Agents Chemother 34(12):2364–2368. https://doi.org/10.1128/aac.34.12.2364
25. Yang X, Ma Z, Zhou S, Weng Y, Lei H, Zeng S et al (2016) Multiple drug transporters are involved in renal secretion of entecavir. Antimicrob Agents Chemother 60(10):6260–6270. https://doi.org/10.1128/aac.00986-16
26. Zhou XJ, Swan S, Smith WB, Marbury TC, Dubuc-Patrick G, Chao GC et al (2007) Pharmacokinetics of telbivudine in subjects with various degrees of renal impairment. Antimicrob Agents Chemother 51(12):4231–4235. https://doi.org/10.1128/aac.00557-07