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Effect of Renal Impairment on the Pharmacokinetics, Safety, and Tolerability of Pudexacianinium (ASP5354) After IV Administration, a Mechanistic Exploration

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INTRODUCTION

- Ureteral injuries which occur during abdominopelvic surgery can potentially lead to severe complications including urinary fistula, sepsis, acute renal failure, and even death[1–3]
- Pudexacianinium chloride (ASP5354) is a new chemical entity that is photo-optically similar to indocyanine green (excitation/emission at 780/820 nm) with unique hydrophilic properties through conjugation with cyclodextrin
- Pudexacianinium is currently being developed as an imaging agent for intraoperative ureter visualization
- Phase 1 studies (NCT03698305 and NCT04878471) in healthy volunteers suggested that the hydrophilic properties of pudexacianinium facilitate near-complete urinary excretion without metabolism[4]

OBJECTIVES

- Part 1 of this study investigated transport of pudexacianinium by major renal drug transporters in vitro
- Part 2 (an open-label, parallel group, single-dose, phase 1 clinical study; NCT05495581) evaluated the pharmacokinetics, safety, and tolerability of a single dose of pudexacianinium in participants with renal impairment versus healthy participants with normal renal function

STUDY DESIGN AND METHODS

In vitro study

- To determine the corrected apparent permeability coefficient ratio (CP_R) of [^{14}C] pudexacianinium, transcellular transport across pig kidney epithelial (LLC-PK1) cells expressing P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) versus control cells was examined
- Transporter-mediated uptake of [^{14}C] pudexacianinium was examined using human embryonic kidney (HEK293) cells expressing human organic anion transporter 1 and 3 (OAT1 and OAT3, respectively), organic cation transporter 2 (OCT2), and multidrug and toxin extrusion 1 and 2-K (MATE1 and MATE2-K, respectively) versus control cells

Clinical study

- Participants were admitted to the clinical unit on day −1 and stayed for 4 days and 3 nights (**Figure 1**)
  - On day 1, participants received a single intravenous (IV) dose of 3 mg pudexacianinium followed by plasma and urine sampling periodically for 48 hours

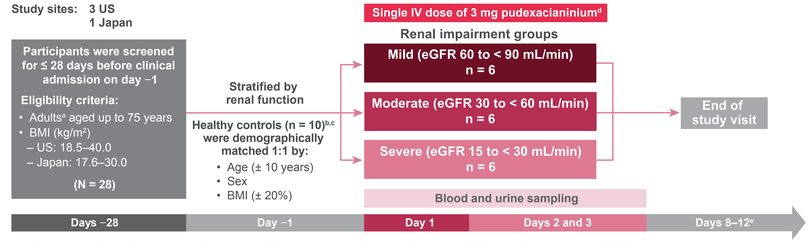
Pharmacokinetic evaluation

- Pudexacianinium was quantified by liquid chromatography-tandem mass spectrometry using CAPCELL PAK ADME-HR columns with a range of 1.00–1000 ng/mL for plasma and 20.0–8000 ng/mL for urine
- Time courses of plasma pudexacianinium concentration and cumulative amount of dose excreted into urine were evaluated
- Plasma protein binding was investigated by ultra-filtration method
- Descriptive statistics were reported for plasma and urine pharmacokinetic parameters
- Geometric least squares mean ratios, reported as percentages, were estimated between pharmacokinetic parameters of each renal impairment group and matched controls
- The relationship between individual estimated glomerular filtration rate (eGFR) and pudexacianinium clearance (total, CL; renal, CL_R) was evaluated by scatter plots

Clinical evaluation

- Safety and tolerability assessments included treatment-emergent adverse events (TEAEs) and urine coloration

Figure 1. Clinical study design and eligibility criteria



[a]Aged ≥ 18 years in the US or ≥ 20 years in Japan; [b]control participants with normal renal function were defined by eGFR ≥ 90 mL/min; [c]control participants could be demographically matched with multiple participants with renal impairment provided matched participants were classed in different groups of renal impairment; [d]on day 1, pudexacianinium was administered with 240 mL water to fasted participants (ie, no calorie intake permitted from ≥ 10 hours predose through 4 hours post-dose); [e]the end of study visit took place 5–9 days after the last pharmacokinetic sample was collected, or at early discontinuation from the study.

BMI, body mass index; eGFR, estimated glomerular filtration rate; IV, intravenous; US, United States.

RESULTS

In vitro study

- The CP_R of [^{14}C] pudexacianinium as a substrate at 1 and 10 µmol/L were 0.7 and 1.4 for P-gp, and 0.8 and 1.3 for BCRP, respectively
- Cleared volumes of [^{14}C] pudexacianinium at 1 and 10 µmol/L into cells expressing OAT1, OAT3, OCT2, MATE1, and MATE-2K were comparable to control cells

Clinical study

- A total of 28 participants (6 participants each with mild, moderate, or severe renal impairment, plus 10 matched controls) were enrolled
  - Demographics were similar across renal function groups (**Table 1**)

Pharmacokinetics

- The maximum concentration (C_{max}) in plasma was comparable between renal impairment groups and matched control groups (**Table 2**)
- Pudexacianinium elimination from plasma slowed as renal impairment worsened (**Figure 2**)
  - Systemic pudexacianinium exposure increased as renal impairment worsened, with area under the curve from dosing to time infinity (AUC_{inf}) geometric least squares mean ratios of 153% (mild), 230% (moderate), and 369% (severe) in the 3 renal impairment groups versus matched control groups
- Plasma protein binding was independent of time and pudexacianinium concentration for all renal function groups
  - The average geometric mean of the fraction unbound (f_u) in plasma was approximately 0.8 across pudexacianinium concentrations and renal function groups
- Renal excretion of pudexacianinium decreased as renal impairment worsened (**Figure 3**)
  - Except for the severe renal impairment group, most pudexacianinium was eliminated into urine within the first 24 hours
  - Over the 48-hour sample collection interval, 64% of the administered dose was recovered as unchanged drug in urine from the severe renal impairment group, and about 90% or greater was recovered in the mild and moderate renal impairment groups and the matched control groups (**Figure 3**; **Table 3**)
- Mean CL_R (**Table 3**) was nearly equivalent to the mean CL (**Table 2**) in all renal function groups except for the severe renal impairment group, driven largely by data from 1 participant in the group who had very low renal clearance
- CL_R and CL increased with increasing individual eGFR (**Figure 4**)

Safety and tolerability

- Pudexacianinium was generally well tolerated regardless of renal function
  - TEAEs of diarrhea, headache and oropharyngeal pain, or hyperbilirubinemia (mild severity) were reported by 1 participant each in the matched control group; abdominal distension and flatulence (moderate severity) were reported by 1 participant in the moderate renal impairment group; and anemia (mild severity) was reported by 1 participant in the severe renal impairment group
  - TEAEs of headache and hyperbilirubinemia were considered related to pudexacianinium by the investigator. All other TEAEs were considered unrelated to pudexacianinium
- Green coloration of urine was observed in 12 (43%) participants: 5 (50%) in the matched control group; 3 (50%) in the mild, 3 (50%) in the moderate, and 1 (17%) in the severe renal impairment groups
  - Duration of the coloration increased as renal impairment worsened, corresponding to longer terminal elimination half-life ($t_{1/2}$)

CONCLUSIONS

- In vitro experiments suggest that pudexacianinium is not a substrate of major renal drug transporters
- Mean plasma C_{max} results were comparable between renal impairment groups and the respective matched control groups
- Systemic pudexacianinium exposure increased as renal impairment worsened
- The mean CL_R of pudexacianinium was comparable with the eGFR of unbound drug (f_u x eGFR), suggesting that glomerular filtration greatly contributed to pudexacianinium elimination
- Single IV doses of 3 mg pudexacianinium appeared well tolerated with mostly mild safety signals in participants with renal impairment or with normal renal function
  - Given the safety profile, surgical patients with moderate or severe renal impairment can be included in phase 3 studies to evaluate the clinical utility of pudexacianinium in this population

Table 1. Participant demographics and baseline characteristics

Renal function	Mild impairment (n = 6)	Matched-mild control (n = 6)[a]	Moderate impairment (n = 6)	Matched-moderate control (n = 6)[a]	Severe impairment[b] (n = 6)	Matched-severe control (n = 6)[a]	Control 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 (%)								
White	4 (66.7)	4 (66.7)	5 (83.3)	4 (66.7)	4 (66.7)	4 (66.7)	7 (70.0)	20 (71.4)
Black/African American	2 (33.3)	0 (0)	1 (16.7)	0 (0)	1 (16.7)	0 (0)	0 (0)	4 (14.3)
Asian	0 (0)	2 (33.3)	0 (0)	2 (33.3)	1 (16.7)	2 (33.3)	3 (30.0)	4 (14.3)
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/m²), 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; [b]one participant with severe renal impairment and suspected extravascular administration was excluded from the pharmacokinetic analysis set.

BMI, body mass index; SD, standard deviation.

Table 2. Plasma pharmacokinetic parameters of total pudexacianinium by renal function group

Category/Statistic		Mild impairment (n = 6)	Matched-mild control (n = 6)[a]	Moderate impairment (n = 6)	Matched-moderate control (n = 6)[a]	Severe impairment (n = 5)[b]	Matched-severe control (n = 6)[a]	Control 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
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
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
$t_{½}$ (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

Plasma pharmacokinetic parameters were estimated using the Phoenix® WinNonlin® version 8.3 (Certara, NJ, USA).

[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 of dosing to time infinity; AUC_{last}, AUC from time of dosing to the last measurable concentration; CL, clearance; C_{max}, maximum concentration; 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 phase.

Table 3. Urine pharmacokinetic parameters of total pudexacianinium by renal function group

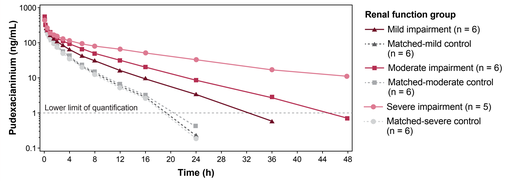
Category/Statistic		Mild impairment (n = 6)	Matched-mild control (n = 6)[a]	Moderate impairment (n = 6)	Matched-moderate control (n = 6)[a]	Severe impairment (n = 5)[b]	Matched-severe control (n = 6)[a]	Control total (n = 10)
Ae_{inf} (mg)	Mean (SD)	2.70 (0.809)	2.69 (0.736)	2.98 (0.395)	2.80 (0.350)	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 the Phoenix® data wizard (WinNonlin® version 8.3, Certara, NJ, USA).

[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.

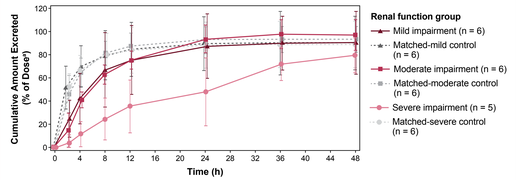
%CV, percent coefficient of variation; Ae_{inf}, cumulative amount of unchanged drug excreted in urine from time of dosing to time infinity after single dose; Ae_{inf}%, Ae_{last} as a percentage of total cumulative amount of unchanged drug excreted in urine; Ae_{last}, cumulative amount of unchanged drug excreted in urine from time of dosing to the last measurable amount; Ae_{last}%, Ae_{last} as a percentage of total cumulative amount of unchanged drug excreted in urine; CL_R, renal clearance; SD, standard deviation.

Figure 2. 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.

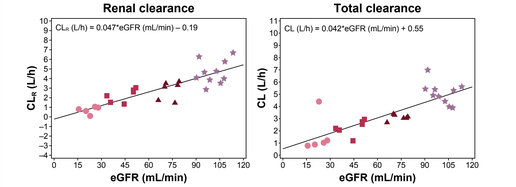
Figure 3. Mean cumulative percentage of pudexacianinium dose excreted into urine, by renal function group



Some participants with normal renal function served as matched controls for multiple participants with renal impairment. The variability in urinary elimination in the severe renal impairment group could be attributed to 1 participant who showed a much lower cumulative amount excreted into urine compared with other participants in the severe renal impairment group.

[a]Error bars represent standard deviation.

Figure 4. Pharmacokinetic relationship between renal and total clearance of pudexacianinium and eGFR



CL, clearance; CL_R, renal clearance; eGFR, estimated glomerular filtration rate.

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