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ORIGINAL ARTICLE

Polyethylene glycol loxenatide (PEX168) in subjects with renal impairment: A pharmacokinetic study

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Aims: Type 2 diabetes mellitus (T2DM) is commonly complicated by renal impairment. Polyethylene glycol loxenatide (PEX168) is a novel long-acting glucagon-like peptide-1 receptor agonist for T2DM. PEX168 pharmacokinetics was studied to identify requirements for dose-modification in T2DM complicated by renal impairment.

Methods: This was a single-centre, open-labelled, parallel-group, single-dose, phase I clinical trial of patients with mild and moderate renal impairment, and with or without T2DM. Age-, sex- and body mass index-matched subjects with normal renal function, and with or without T2DM were recruited as controls. Subjects received a single abdominal subcutaneous injection of PEX168 200 μg. Pharmacokinetic samples were taken at 0, 24, 48, 72, 96, 120, 144, 216, 312, 480, 648 and 720 hours.

Results: Twenty-three patients were included in the pharmacokinetics analysis. Vz/F and CL/F were lower in the moderate impairment group than in the other groups. The mean $t_{1/2}$ (163 hours) in the moderate impairment group was prolonged compared to the mild impairment (117 hours) and normal (121 hours) groups. AUC_{0-inf} increased by 13 and 100.7% in patients with mild and moderate renal impairment, respectively. Most adverse events were mild gastrointestinal disorders, with only 1 serious adverse event observed.

Conclusion: A single dose of 200 μg of PEX168 was in general well tolerated in patients with renal impairment. The in vivo clearance rate of PEX168 in patients with moderate renal impairment is slower than in patients with mild renal impairment and normal renal function and dose adjustment might be required (ClinicalTrials.org #NCT02467790).

The authors confirm that the PI for this paper is Jianwen Wang and that he had direct clinical responsibility for patients.

[†]These authors contributed equally to this work.

KEYWORDS

chronic kidney disease, pharmacokinetics, phase I trial, polyethylene glycol loxenatide, type 2 diabetes mellitus

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is an endocrine disorder characterized by hyperglycaemia resulting from variable degrees of insulin resistance and deficiency.[1] The worldwide prevalence of T2DM is estimated at 500 million in 2018.[2] In China, the prevalence of T2DM and prediabetes were estimated at 10.9 and 35.7%, respectively, in 2013.[3] T2DM is manageable using glucose-lowering agents, but is nevertheless associated with increased mortality from multiple causes.[4] About 20–40% of patients with T2DM also have diabetic nephropathy, which is the major reason for renal failure in these patients. By contrast, chronic kidney disease (CKD) also complicates T2DM treatment since some drugs are not appropriate in CKD.

With the ability to promote insulin secretion in a glucose-dependent manner, **glucagon-like peptide-1** (GLP-1) and its receptor agonist (GLP-1RA) exenatide (synthetic exendin-4) are becoming the focus of studies on novel hypoglycaemic agents. As GLP-1 has a short in vivo half-life due to its rapid degradation by **dipeptidyl peptidase-4** (DPP-4), multiple and repeated administrations are required for treatment effect. Compared with naturally occurred GLP-1, exenatide is not so easily degraded by DPP-4 and is characterized by longer half-life than GLP-1 and potent bioactivity. Nevertheless, as a peptide agent, exenatide still has a limited in vivo half-life of 2–3 hours and requires subcutaneous injections twice a day, which affects patient compliance.

PEX168 is a 44.2-kDa long-acting GLP-1RA that is obtained by modifying the chemical structure of exendin-4 on the 2nd (glycine alanine), 14th (methionine norleucine), 28th (asparagine glutamine) and 39th (serine cysteine) N-terminal positions, in addition to modification of the branched polyethylene glycol. Available data suggest that compared to exenatide, PEX168 can further resist rapid degradation by DPP-4 and might reduce toxicity and antigen immunity, possibly leading to longer half-life and acting duration, increased bioavailability, and enhanced treatment effects. With longer dosing interval and fewer dosing times, patient compliance could be potentially improved with PEX168. Previous studies showed that long-term administration of PEX168 at 100–200 μg not only significantly improves haemoglobin A1c levels and fasting and postprandial blood glucose concentrations in T2DM patients, but also has better safety and tolerability than the 300-μg regimen.

Our preclinical study shows that the kidney is the major excretion organ of PEX168. Renal impairment could alter the pharmacokinetics of PEX168, and in turn affect its efficacy and safety. Given that the use of PEX168 in patients with diabetic nephropathy and diabetic patients complicated with kidney diseases is a long-term regimen, the aim of the present study was to assess whether or not it is necessary to adjust the dose of PEX168 for patients with renal impairment (ClinicalTrials.org #NCT02467790).

What is already known about this subject

- Diabetes mellitus (DM) is commonly complicated by renal impairment.
- Polyethylene glycol loxenatide (PEX168) is a novel long-acting glucagon-like peptide-1 receptor agonist for type 2 DM.

What this study adds

- In vivo clearance rate of PEX168 in subjects with moderate renal impairment is slower than in subjects with normal or mildly impaired renal function.
- The adverse events were mainly mild systemic and gastrointestinal symptoms.
- Dose reduction might be required for patients with moderate renal function impairment.

2 | METHODS

2.1 | Study design and subjects

This was a single-centre, open-labelled, parallel-group, single-dose, phase I clinical trial of patients with mild and moderate renal impairment, and with or without T2DM (ClinicalTrials.org # NCT02467790). After the initial enrolment, age-, sex- and body mass index-matched (as far as possible) subjects with normal renal function, and with or without T2DM were recruited as controls. The study was approved by the Ethics Committees of each centre and was in line with the Helsinki Declaration and the Good Clinical Practice. All patients provided signed informed consent before participation.

The inclusion criteria for the patients with renal impairment were: age 31–65 years, with or without T2DM; ≥50 kg for males, ≥45 kg for females, body mass index 18–28 kg/m^2; CKD stage 2 (Cockcroft–Gault creatinine clearance [CLcr] 60–89 mL/min) or 3 (CLcr 30–59 mL/min), using the Kidney Disease Outcomes Quality Initiative classification; agreed to quit smoking, alcohol, caffeine and fruit juice from 48 hours before the trial to the end of the trial; and understood the study protocols and methods. The inclusion criteria for controls were: age 31–65 years, with or without T2DM; ≥50 kg for males, ≥45 kg for females, body mass index 18–28 kg/m^2; CLcr ≥90 mL/min; agreed to quit smoking, alcohol, caffeine and fruit juice

from 48 hours before the trial to the end of the trial; and understood the study protocols and methods. The exclusion criteria for the patients with renal impairment were: allergy to GLP-1 agents or history of GLP-1RA, GLP-1 analogue, DPP-4 inhibitor or any other agents with similar structures; acute diseases involving any other organs or any chronic diseases that may affect the in vivo process of the study drug, other than renal impairment; history of any surgeries within 6 months; blood donation of ≥400 mL within 3 months or blood transfusion within 1 month; participation in any clinical trial within 3 months; alcohol, tobacco, drug or substance abuse; abnormal laboratory results with clinical significance other than those caused by renal impairment; positive pregnancy test result, pregnancy, lactating or plan to be pregnant within 6 months, or those who could not use effective contraception during the trial; positive hepatitis B surface antigen, hepatitis C antibody, human immunodeficiency virus antibody, or syphilis antibody; or could not complete the trial or might be subjected to significant risks if they participated in the trial as considered by the investigators.

In addition to the above criteria, the additional exclusion criteria for the controls were: (i) history of chronic diseases involving the cardiovascular, neuropsychiatric, digestive, respiratory, urinary, endocrine, or the other systems before the screening; (ii) urea nitrogen > normal range; or (iii) positive for urinary protein.

2.1.1 | Intervention

Based on the results from the phase I pharmacokinetic (PK) trial of PEX168 in patients with T2DM and normal renal function,[12] PEX168 exhibits linear PK and the maximum effective dose is 200 μg/week with an acceptable safety profile; therefore, the dose selected for PEX168 in the present study was 200 μg. Eligible patients were transferred to the trial ward or the nephrology ward 1 day before dosing. On the dosing day, blank blood samples were harvested before dosing; after that, subjects received a single abdominal subcutaneous injection of PEX168 200 μg (0.5 mL: 0.2 mg, Jiangsu Hansoh Pharmaceutical Group Co., Ltd.) at 08:00. After the injection, all subjects immediately were asked to have the same standard breakfast and then received examinations and PK blood sampling at the wards. There were no requirements about water consumption before drug injection. Drugs lowering blood glucose, or known to affect blood glucose (e.g. oestrogens, oral contraceptives, phenytoin, niacin, sympathomimetics, thyroid drugs, soniazid, corticosteroids, growth hormone drugs, drugs that may cause weight loss, drugs known to cause adverse reactions to the gastrointestinal, drugs with common toxicity to major organs, and any drug deemed to interfere with the interpretation of the efficacy and safety of PEX168) track were prohibited during the study period.

PK blood sampling (3 mL) was conducted just before dosing (day 1) and at 24 hours (day 2), 48 hours (day 3), 72 hours (day 4), 96 hours (day 5), 120 hours (day 6), 144 hours (day 7), 216 hours (day 10), 312 hours (day 14), 480 hours (day 21), 648 hours (day 28) and 720 hours (day 31) after dosing. Blood samples were collected in coagulation tubes. After centrifugation, the serum samples were stored at −20° or −70°C until analysis.

2.1.2 | Measurement of PEX168

Concentrations of PEX168 in the serum samples were determined by enzyme-linked immunosorbent assay (ELISA, Covens Pharmaceutical R&D [Shanghai] Co., Ltd.). The range of the calibrated standard curve concentrations was 12.50–800.00 ng/mL and a 4-parameter logistic model with a weight coefficient of $1/Y^2$ was used for the nonlinear regression analysis. The lower limit of quantification (LLOQ) of PEX168 was 12.50 ng/mL. All sample concentrations below the LLOQ were recorded as below the limit of quantification (BLQ). The between-day measurement accuracy of the quality control (QC) concentrations was expressed as % bias and ranged from −3.5 to 3.4% for low- (32.00 ng/mL), moderate- (160 ng/mL) and high-concentration (640 ng/mL) QC samples. The between-day measurement precision of the QC sample concentrations was expressed as coefficient of variation (CV%) and were no higher than 19.6% for low-, moderate-, and high-concentration QC samples.

2.1.3 | Endpoints and evaluation

PK parameters were calculated using a noncompartmental analysis using the Phoenix WinNonlin software (Pharsight, Mountain View, CA, USA; version 6.4). The main PK parameters included the maximal observed drug concentration (C_{max}), the time of C_{max} (T_{max}), area under the plasma concentration–time curve from 0 hours to the last time point of blood sample collection (AUC_{0-t}, linear up/log down method), the area under the plasma concentration–time curve from time 0 extrapolated to infinity (AUC_{0-inf}), the half-life ($t_{1/2}$), the apparent volume of distribution (Vz/F) and the apparent renal clearance (CL/F). As the doses mentioned in the clinical dosing regimen and clinically administered doses were calculated based on the polypeptide content, all the PEX168 concentrations in the current study were also calculated based on the polypeptide content.

2.1.4 | Safety

The safety evaluation during the trial was based on monitoring adverse events (AEs), vital signs, clinical laboratory tests, physical examinations and 12-lead electrocardiograms. Time points for safety evaluation included 24 hours (day 2), 144 hours (day 7), 312 hours (day 14) and 720 hours (day 31) after dosing. The evaluation included monitoring of vital signs, physical examinations, fasting venous blood glucose, blood routine, urine routine, and blood biochemistry or 12-lead electrocardiograms. Patient-reported AEs were recorded on all days of blood collection.

2.1.5 | Statistical analysis

Continuous data were expressed as means ± standard deviation or medians (range), as appropriate. Categorical data were expressed as number of cases (n) and percentage. Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NY, USA). Two-sided *P*-values <.05 were considered statistically significant.

The PK analysis was based on the time-dependent or logarithmic plot of blood PEX168 concentration. Results of the main PK parameters from the analysis for the concentration–time curves of the 3 groups were summarized as *n*, mean, standard deviation, CV, geometric mean and geometric CV. Variance analysis for the AUC_{0-inf} and C_{max} of PEX168 from the 3 groups was conducted after logarithmical conversion. If the 90% confidence intervals (CIs) of the geometric mean ratios of AUC_{0-inf} and C_{max} from the renal impairment group to the of normal renal function group fell within the 0.80 and 1.25 boundaries, the PK changes of the 2 groups were deemed as the same. The PK analysis data set included all subjects who used the study drug, had available data for postdosing PK evaluation, and did not have significant protocol deviation affecting the PK analysis. The safety analysis data set included all subjects who used the study drug and had available data for postdosing safety evaluation.

2.1.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[13] and are permanently achieved in the Concise Guide to PHARMACOLOGY 2017/2018.[14]

TABLE 1 Baseline characteristics

Variable	Normal renal function (*n* = 10)	Mild renal impairment (*n* = 8)	Moderate renal impairment (n = 8)
Age (y), mean ± SD	38.5 ± 9.2	47.8 ± 10.7	47.8 ± 11.4
Male, *n* (%)	10 (100.0%)	7 (87.5%)	5 (62.5%)
Han, *n* (%)	8 (80.0%)	8 (100.0%)	8 (100.0%)
Height (cm), mean ± SD	166.0 ± 6.2	164.4 ± 4.8	162.6 ± 6.0
Weight (kg), mean ± SD	63.7 ± 4.9	66.6 ± 7.2	61.8 ± 9.6
BMI (kg/m^2), mean ± SD	23.2 ± 1.9	24.6 ± 2.3	23.3 ± 3.0
CLcr (mL/min), mean ± SD	99.4 ± 9.8	75.4 ± 8.7	44.5 ± 8.2

BMI, body mass index; CLcr, creatinine clearance; SD, standard deviation.

3 | RESULTS

3.1 | Subjects

Of the 94 subjects who were initially screened, 26 (22 males and 4 females) were enrolled, including 10 subjects with normal renal function and 8 each with mild and moderate renal impairment. Table 1 lists their demographic data. Apart from age, all the baseline characteristics were comparable among the groups. Except for 3 T2DM patients in the mild renal impairment group, all other subjects were nondiabetic.

A total of 25 subjects (22 males and 3 females) completed the study and 23 were included in the PK analysis. Reasons for exclusion from PK analysis included wrong enrolment in the normal renal function group (*n* = 2, CLcr <90 mL/min) and voluntary withdrawal due to a serious AE (SAE, *n* = 1, with moderate renal dysfunction).

3.2 | PK

The PK parameters and the geometric mean concentration–time profiles following subcutaneous administration are shown in Table 2 and Figure 1, respectively. Mean clearance rate of PEX168 was reduced in the moderate impairment group (CL/F and Vz/F: 0.00711 L/h and 1.69 L) compared to the normal (CL/F and Vz/F: 0.0136 L/h and 2.28 L) and mild impairment (CL/F and Vz/F: 0.0140 L/h and 2.44 L) groups. Accordingly, the mean $t_{1/2}$ (163 hours) in the moderate impairment group was prolonged compared to the mild impairment (117 hours) and normal groups (121 hours). Compared to the normal group, the in vivo median PEX168 T_{max} in the mild impairment group was increased from 96 to 120 hours, the AUC_{0-inf} was only increased by 13.1% (estimated ratio: 113% [90%CI: 82.1%–156%]) and the C_{max} was reduced by 14.3% (85.6% [90%CI: 61.5%–119%]). Compared to the normal group, the in vivo median PEX168 T_{max} in the moderate impairment group was increased from 96 to 144 hours, the AUC_{0-inf} was increased by 100.7% (estimated ratio: 201% [90%CI: 144%–280%]), and the C_{max} is increased by 29.1% (estimated ratio: 129% [90%CI: 91.7%–182%]; Table 3).

3.3 | Safety

Treatment-emergent AEs and all-cause AEs are shown in Table 4 and Supplementary Table S1, respectively. The overall occurrence of AEs didn't increase with increased degree of renal function impairment.

TABLE 2 Geometric means of the pharmacokinetic parameter of PEX168 by renal function

Grouping	n	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)	AUC_% Extrap (%)	AUC_{0-inf} (h*ng/mL)	Vz/F (L)	CL/F (L/h)
Normal	8	121 ± 13.6	114 ± 45.8	58.4 ± 14.6	14 200 ± 2730	2.38 ± 0.60	14 600 ± 2790	2.44 ± 0.56	0.0140 ± 0.00298
Mild impairment	8	117 ± 16.5	123 ± 15.4	54.1 ± 29.7	15 900 ± 10 400	3.49 ± 1.32	16 500 ± 10 900	2.28 ± 1.09	0.0136 ± 0.00657
Moderate impairment	7	163 ± 14.7	144 ± 33.9	78.1 ± 35.9	27 200 ± 8300	6.92 ± 1.75	29 200 ± 8930	1.69 ± 0.61	0.00711 ± 0.00220

AUC_{0-inf}, area under the plasma concentration–time curve from 0 hours extrapolated to infinity; AUC_{0-t}, area under the plasma concentration–time curve from 0 hours to the last time point of blood sample collection; AUC_% Extrap, area under the plasma concentration curve extrapolation; CL/F, apparent renal clearance; $C_{max,}$ maximal observed drug concentration; $T_{1/2}$, half-life; $T_{max,}$ time of C_{max}; Vz/F, apparent volume of distribution.

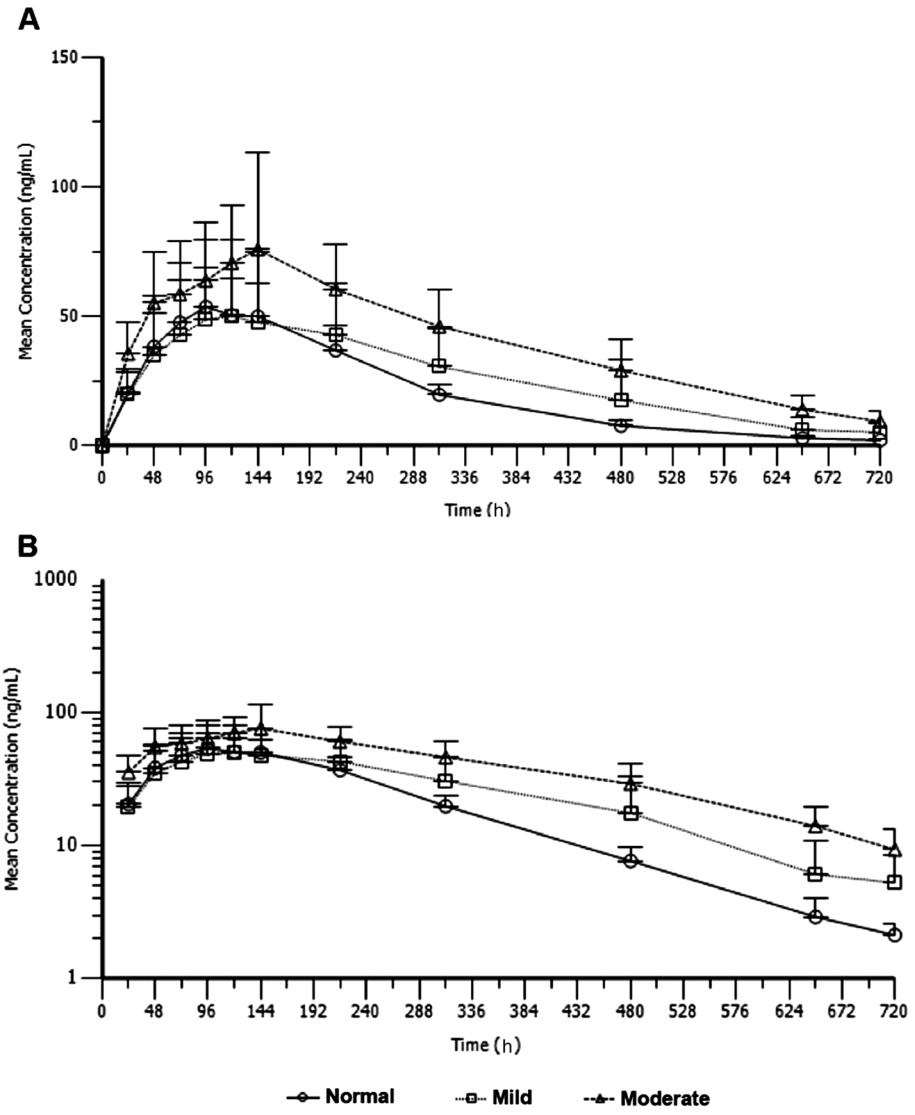

FIGURE 1 Pharmacokinetics of PEX168 by renal function. (A) Mean (SD) plasma concentration–time profiles of PEX168 after a single dose. (B) Mean (SD) plasma concentration–time profiles of PEX168 after a single dose (logarithmic curve). Data are presented for the pharmacokinetics set. SD, standard deviation

TABLE 3 Analysis of the means of pharmacokinetic parameters among groups

	Geometric mean			Geometric mean ratio (%) normal *vs* mild			Geometric mean ratio (%) normal *vs* moderate		
Parameter	Normal (*n* = 8)	Mild impairment (*n* = 8)	Moderate impairment (*n* = 7)	Ratio	90%CI lower limit	90%CI upper limit	Ratio	90%CI lower limit	90%CI upper limit
AUC_{0-inf} (h*ng/mL)	14 600	16 500	29 200	113	82.1	156	201	144	280
C_{max} (ng/mL)	56.6	48.5	73.1	85.6	61.5	119	129	91.7	182

AUC_{0-inf}, area under the plasma concentration–time curve from 0 hours extrapolated to infinity; C_{max}, maximal observed drug concentration.

No noteworthy AE was observed except for 1 SAE in the moderate impairment group. The most common AE observed for all groups were gastrointestinal disorders (80.8%), followed by metabolism and nutrition disorders (42.3%), and laboratory tests (42.3%). The most common treatment-emergent AEs were also gastrointestinal disorders for all groups (80.8%), including nausea, vomiting and bloating. The SAE was considered to be drug-related by the study investigators. It was observed in a subject with stage 3 CKD from the moderate impairment group who suffered from long-term symptoms of nausea and vomiting (10 days) and was admitted for acute kidney injury. All other subjects only had short-term gastrointestinal disorders that spontaneously resolved within 1–2 days.

4 | DISCUSSION

Current GLP-1RAs suffer from short half-life and poor compliance. PEX168 has longer half-life and acting duration, increased

TABLE 4 Treatment-emergent adverse events (AEs)

	Normal (*n* = 10)		Mild impairment (*n* = 8)		Moderate impairment (*n* = 8)	
MedDRA	***n***	**%**	***n***	**%**	***n***	**%**
Overall AEs	7	70	7	87.5	7	87.5
Nausea	2	20	4	50	8	62.5
Vomiting	0	0	4	50	5	50
Bloating	5	50	2	25	0	0
Hiccup	0	0	1	12.5	1	12.5
Abdominal discomforts	1	10	0	0	0	0
Retching	0	0	0	0	2	12.5
Increased white blood cell count	0	0	0	0	1	12.5
Oropharyngeal discomfort	0	0	1	12.5	0	0
Acute kidney injury	0	0	0	0	1	12.5
Anaemia	0	0	0	0	1	12.5

bioavailability, and may therefore enhance treatment effects, but its pharmacokinetics in renal impairment are unknown. For drugs (or metabolites) that can be secreted or metabolized by the kidneys, the 2005 Chinese *Technical guidelines for PK studies in patients with impaired renal function* recommend PK studies in patients with renal impairment. Therefore, this study aimed to assess whether or not it is necessary to adjust the dose of PEX168 for patients with renal impairment. The results suggest that the in vivo clearance rate of PEX168 in patients with moderate renal impairment is slower than in patients with mild renal impairment and normal renal function.

Results from studies on GLP-1 analogues such as exenatide, liraglutide, albiglutide, and dulaglutide show that mild or moderate renal impairment does not significantly affect their in vivo PK and that no dose adjustment is required. By contrast, a study showed that the usual doses of exenatide were not appropriate for patients with severe renal impairment and end-stage kidney disease.[20] Our results showed that mild renal impairment has little impact on the PK profiles of PEX168. However, moderate renal impairment decreased the clearance rate of PEX168 and significantly increased subject exposure to PEX168. Compared with subjects with normal renal function, AUC_{0-inf} and C_{max} were increased by 100.7 and 29.1% respectively in subjects with moderate renal impairment.

In terms of safety, PEX168 was in general well-tolerated in patients with mild-to-moderate renal function impairment, with no trend of increased AEs with increased level of renal function impairment, similar to other GLP-1RAs. The most common AE observed in each group were gastrointestinal disorders (80.8%), followed by metabolism and nutrition disorders (42.3%), and laboratory tests (42.3%). After the abdominal subcutaneous administration of 200 μg of PEX168 on a fasting stomach on day 1, 16 subjects with mild or moderate renal impairment and 10 subjects with normal renal function had AEs mainly that occurred 1–2 days after injection. The AEs were mainly mild systemic and gastrointestinal symptoms such as nausea, vomiting and fatigue, and were consistent with previous trials.

In addition, the presence or absence of drug-related nephrotoxicity is a critical clinical issue safety. Peptide agents such as GLP-1RAs are mainly degraded in vivo into amino acids, thus producing no direct nephrotoxic effect. Correlation between marketed GLP-1RAs and kidney injury has been reported previously, mainly exenatide. In most cases, the acute kidney injury probably resulted from loss of fluid volume and reduction in fluid intake mainly as a result of nausea and vomiting induced by exenatide. Liraglutide has also been reported to potentially cause acute kidney injury,[24] as well as albiglutide and durapeptide.[9] The structure of the bioactive component losenalide in PEX168 is close to that of exendin-4. In addition, polyethylene glycol is added to the structure of losenalide to prolong the half-life and reduce immunogenicity. In the present study, 1 subject with moderate renal impairment had acute kidney injury within 3 days after PEX168 administration. The acute kidney injury was caused by hypovolaemia as a result of moderate nausea and vomiting. After active treatment, patient's creatinine levels were restored to the baseline levels and nausea and vomiting were relieved within 2 weeks. This case of acute kidney injury was considered of a prerenal origin. In 2 previous trials (monotherapy and combination therapy with metformin, respectively), 1 AE of proteinuria occurred in the placebo group in each trial. The incidence rate of renal-related AEs was similar between the treatment groups of the 2 trials. Taken together, the results do not suggest that PEX168 damages renal function.

The present study has limitations. In principle, 7 groups of kidney function (normal, mild impairment, moderate impairment, nondialysis subjects with severe renal impairment, nondialysis subjects with end-stage renal disease, subjects with severe renal impairment requiring dialysis, and subjects with end-stage renal disease requiring dialysis) should be recruited in order to obtain a complete picture of the renal effect of PEX168, but it would be very difficult to enrol the latter 4 types of patient and GLP-1 is mainly used in early-stage T2DM patients with residual β islet function. In addition, PEX168 is to be used in patients with T2DM, but the subjects recruited here did not have T2DM due to safety considerations. Whether renal CL is saturable in patients was not assessed in the present study, and we did not investigate the possibly involved renal transporters. In addition, hepatic clearance was not determined. Nevertheless, in *in vivo* experiments in rats,

after subcutaneous injection of ^{125}I-Tyr-PEX-168 (50.0 μg/rat), the radioactive agent was mainly excreted from the urine and faeces, with >82% of the injected radioactivity excreted within 264 hours. Furthermore, the differences between men and women are unknown, with only a few women included in the present study. Finally, 2 subjects were incorrectly enrolled and had to be excluded in the PK analysis.

In vivo clearance rate of PEX168 in subjects with moderate renal impairment is slower than in subjects with normal or mildly impaired renal function. The AEs were mainly mild systemic and gastrointestinal symptoms. Dose reduction might be required for patients with moderate renal function impairment.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

G.Y. and H.Z. designed and planned the study. J.W., J.H., W.L., S.T., J.S., X.Z., J.L., B.Y., J.L., X.Z., Q.Y. collected and analyzed the data. X. Y. and S.Y. performed the statistical analyses. J.W. and H.Z. drafted the paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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