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ORIGINAL RESEARCH

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenous Administration JMKX003142 in Chinese Healthy Subjects: A Randomized, Double-Blind, Placebo-Controlled, Single, and Multiple Ascending Dose Phase I Clinical Trial

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Purpose: This study is the first-in-human study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) profiles of single ascending doses (SAD) and multiple ascending doses (MAD) of JMKX003142 injection in healthy Chinese subjects.

Patients and Methods: In this Phase I, randomized, double-blind, placebo-controlled study, 48 subjects in the SAD (0.1–6 mg) study received intravenous injection of JMKX003142 or placebo in ascending dose. Thirty subjects in the MAD (1–4 mg) study received an intravenous injection of JMKX003142 or placebo once a day for five consecutive days. The primary endpoint was the safety and tolerability of JMKX003142 injection, with the secondary and exploratory endpoints focusing on its PK and PD profiles, respectively.

Results: The JMKX003142 injection exhibited favourable safety and tolerability, with all treatment-emergent adverse events (TEAEs) being mild. No serious adverse events, deaths or discontinuations due to TEAEs were observed. Following single and multiple intravenous injections of JMKX003142, the maximum concentration (C_{max}) and area under plasma concentration–time curve (AUC) of JMKX003142 and its metabolites increased with dose level, with increases in C_{max} being dose-proportional. In 1 mg or higher dose group of SAD study, the mean terminal half-life ($t_{1/2}$) of JMKX003142 was between 5.2 and 12.7 h. Following multiple intravenous injections of JMKX003142, the $t_{1/2}$ of JMKX003142 was determined to range from 11.1 and 11.8 h. Moreover, JMKX003142 demonstrated favourable PD profiles following both single and multiple intravenous injections. The evaluation of the daily cumulative urine volume indicated that the diuretic effect of the JMKX003142 injection was evident at doses of 1 mg and above, with effects intensifying at higher doses.

Conclusion: Overall, both single and multiple intravenous injections of JMKX003142 have been demonstrated to be safe, well tolerated, and to possess excellent PK characteristics as well as significant diuretic activity.

Trial Registration: This study was registered with ClinicalTrials.gov (NCT06344533).

Keywords: active arginine vasopressin V_2 receptor antagonist, JMKX003142, safety, tolerability, pharmacokinetics, pharmacodynamics

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Introduction

Heart failure (HF) is a complex clinical syndrome characterized by the failure of the heart to pump blood effectively, accompanied by dyspnea, fatigue and fluid retention.[1] Globally, HF affects over 640,000 individuals, with its prevalence on the rise due to the aging population.[2,3] Statistical evidence reveals that approximately 70% of HF patients manifest fluid retention, a key contributor to reduced quality of life and unfavorable outcomes.[4] The majority of HF patients utilize diuretic medications to alleviate symptoms of congestion, including loop diuretics, thiazide diuretics, and potassium-sparing diuretics.[5] Nevertheless, treatments such as loop diuretics frequently exacerbate renal perfusion, thereby instigating a detrimental cycle of renal function deterioration, recurrent hospitalization and elevated mortality.[6] Furthermore, diuretic resistance to ascending doses of loop diuretics is increasingly common,[7] underscoring the necessity for the exploration of novel diuretic agents.

Arginine vasopressin (AVP) V_2 receptor (V2R) antagonists represent a new generation of diuretics, with tolvaptan serving as the representative pharmaceutical agent within this classification.[8] Tolvaptan has been shown to selectively inhibit the binding of AVP to the V2R in the distal renal tubules, thereby achieving diuresis without inducing electrolyte imbalance or compromising renal function.[9,10] Multiple studies have corroborated the benefits of tolvaptan in mitigating fluid loss and respiratory distress in patients with acute decompensated HF.[11–13] Unfortunately, due to its low aqueous solubility, tolvaptan is only available in oral formulations (tablets and granules). Nevertheless, patients for whom oral administration is not feasible still require diuretic drugs that can be administered intravenously. Such cases include intestinal congestion and edema in patients with acute HF, altered consciousness, impaired oral intake due to mechanical ventilation, or impaired swallowing reflex in elderly patients.[14–16] It is important to note that there is currently no intravenous formulation of V2R antagonists available in China. There is an urgent need for a V2R antagonist intravenous formulation that is not affected by digestive tract absorption disorders and can quickly take effect without intestinal absorption disorders and diuretic resistance.

JMKX003142 injection constitutes an intravenous formulation of innovative selective AVP V2R antagonist, which is capable of selectively inhibiting the V2R that is situated on the basolateral surface of renal tubular cells. This inhibition leads to the promotion of free water excretion without concomitant electrolyte loss, resulting in a decrease in water retention. Preclinical studies (unpublished results) have demonstrated that JMKX003142 inhibits the proliferation of LLC-PK1 cells (a model of renal tubular epithelial cells) in a dose-dependent manner, while also suppressing the volume expansion of human autosomal dominant polycystic kidney disease (ADPKD) renal cyst cells. This avoids the side effects caused by the Hook effect of other drugs, whereby high concentrations promote proliferation. As an intravenous preparation, JMKX003142 injection has the potential to address the current unmet therapeutic needs of patients with fluid retention caused by HF. This first-in-human trial evaluated the safety, tolerability, pharmacokinetic (PK), and pharmacodynamics (PD) profiles of single ascending doses (SAD) and multiple ascending doses (MAD) of JMKX003142 injection in Chinese healthy adult subjects, and provided information to determine the dose regimen in further clinical trials.

Materials and Methods

Study Design

This study was a single-center, randomized, double-blind, placebo-controlled, SAD and MAD Phase I clinical trial. The primary objective of this study was to evaluate the safety and tolerability of single and multiple doses of JMKX003142 injection in healthy subjects. Secondary and exploratory objectives were PK and PD profiles, respectively. This clinical trial was approved by the medical science research ethics committee of Peking University Third Hospital (Approval No: 2024–039-01) and conducted according to the International Conference on harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. This study was registered with ClinicalTrials.gov (NCT06344533).[17] Written informed consent was obtained from each subject before initiation of any study procedures.

This study comprised two parts: the SAD study and the MAD study (Figure 1). In the SAD study, a 27-day screening period, 1-day baseline period, 1-day dosing period, 3-day hospitalization observation period, and a 3-day safety follow-up period were employed. Forty-eight subjects were assigned to six dose-escalation cohorts corresponding to

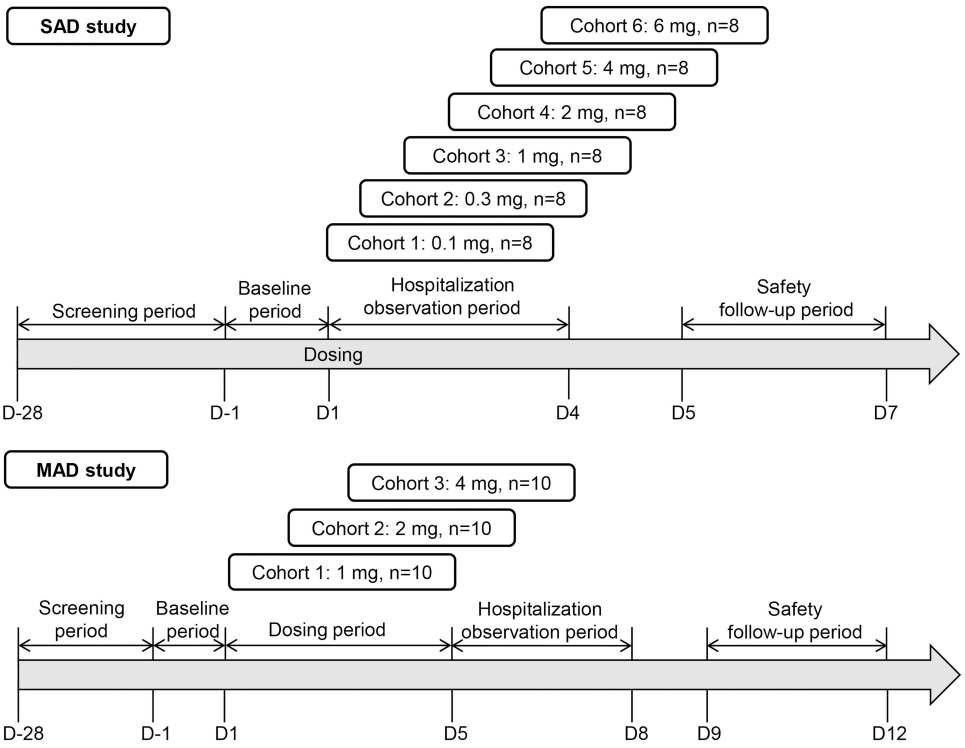

Figure 1 Trial design. The trial was a Phase I, multicenter, participant- and investigator-blinded, placebo-controlled, and randomized, SAD and MAD study of JMKX003142 in healthy participants.
Abbreviations: SAD, single ascending dose; MAD, and multiple ascending doses.

JMKX003142 doses of 0.1, 0.3, 1, 2, 4, and 6 mg. Within each cohort, eight subjects were randomized at a 3:1 ratio to receive either JMKX003142 injection or placebo. In the MAD study, a 27-day screening period, 1-day baseline period, 5-day dosing period, 3-day hospitalization observation period, and a 4-day safety follow-up period were employed. Thirty subjects were randomly assigned to three dose-escalation cohorts, with each cohort designated for JMKX003142 doses of 1, 2, and 4 mg. In each cohort, 10 subjects were randomized in a 4:1 ratio to receive either JMKX003142 injection or placebo.

Given that infusion-related adverse reactions still occurred with tolvaptan sodium phosphate (a product of the same class) even when the administration time was at least 1 h,[18] this study initially explored a 5 min dosing time in the SAD study for the protection of subjects, despite the structural optimization implemented for the JMKX003142 injection. After confirming its safety, the dosing time was further shortened to 2 min in the MAD study. JMKX003142 injection and placebo were administered intravenously in the morning under fasting conditions, with subjects required to fast for at least 10 h overnight and an additional 2 h post-dose. Drinking water was prohibited 1 h before and during the administration, and post-dose intake recorded as needed. The SAD and MAD studies utilized a stepwise dose escalation approach. In the 0.1 mg cohort, the sentinel dosing method was employed: two subjects were initially enrolled and randomly assigned to receive JMKX003142 or placebo, respectively, and following a thorough safety evaluation for a minimum of 72 h post-dose, the remaining six subjects were administered. Initiation of the subsequent dosing group was contingent on the completion of a comprehensive evaluation, which included assessing the safety, tolerability, PK, and PD characteristics of the preceding dosing group.

Subjects

The key inclusion criteria were: 1) healthy subjects aged 18 to 45 years; 2) body mass index (BMI) ranging from 19 kg/m^2 to 28 kg/m^2, with a total body weight of ≥50.0 kg and <90.0 kg for men, and ≥45.0 kg and <90.0 kg for women; 3) subjects with no abnormalities or only clinically insignificant findings were identified through comprehensive physical

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examinations, laboratory tests and electrocardiograms (ECGs). The exclusion criteria for the subjects included but were not limited to 1) have a history of allergies to the investigational drug, any of its components, or other V2R antagonists, or have a history of allergies to other drugs, food, or other substances; 2) having a history of diseases involving the central nervous, cardiovascular, digestive, respiratory, urinary, hematological, endocrine systems, or any other medical conditions deemed unsuitable for participation in the clinical trial by the investigators; 3) subjects who are unable to urinate normally, feel thirsty, or have difficulty consuming fluids or food due to various reasons, as these conditions would impair accurate monitoring of fluid intake and output, thereby compromising both subject safety and the interpretability of PD data; 4) abnormal vital signs, clinical laboratory, or ECGs examinations during screening, such as blood sodium >145 mmol/L or <130 mmol/L, blood potassium >5.5 mmol/L, estimated glomerular filtration rate (eGFR) <90 mL/min/1.73m^2, QTc interval prolongation (QTcF >450 ms for men or QTcF >470 ms for women).

Safety and Tolerability Measurements

Safety and tolerability of JMKX003142 were assessed by monitoring adverse events (AEs), vital sign changes from baseline (temperature, blood pressure, pulse, and respiratory rate), physical examination, clinical laboratory tests (complete blood count, urinalysis, blood biochemistry panel, coagulation function tests, and additional assays), ECGs, body weight, and daily fluid balance (daily fluid intake minus daily cumulative urine volume). AEs were categorized using the Medical Dictionary for Regulatory Activities (MedDRA), employing the System Organ Classification (SOC) and Preferred Term (PT) systems.[19] Treatment-emergent AEs (TEAEs) were defined as AEs that occurs during treatment, and TEAEs were categorized based on severity, duration, clinical outcome and relationship to the drug. The severity of TEAEs was determined according to the classification standards for AEs issued by National Institute on Aging (NIA),[20] which classify events into mild, moderate, and severe based on clinical impact and intervention requirement. Treatment-related AEs (TRAEs) were defined as TEAEs that were related to the drug. If there is a lack of correlation with the drug, it is judged as related.

Pharmacokinetic Assessments

Plasma samples were collected for the PK assessments of JMKX003142 and its metabolites (JMKX003142-M5, JMKX003142-M8-2, and JMKX003142-D4). PK sampling in the SAD study spanned from pre-dose (0 h) to 72 h post-dose. In the MAD study, sampling was performed from pre-dose (0 h) to 24 h post-dose on Day 1 (ie, pre-dose (0 h) on Day 2); at pre-dose (0 h) on Days 3–4; and from pre-dose (0 h) to 72 h post-dose on Day 5. Specifically, for the SAD study, blood samples (4 mL) were collected at pre-dose (0 h), at the end of intravenous injection (5 min), at 10 and 30 min post-dose, and at 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 h post-dose. For the MAD study, blood samples (4 mL) were collected at pre-dose (0 h), at the end of intravenous injection (2 min), at 10 and 30 min post-dose, and at 1, 2, 3, 4, 6, 8, 12, and 24 h post-dose on Day 1; at pre-dose (0 h) on Days 3–4; and at pre-dose (0 h), at the end of intravenous injection (2 min), at 10 and 30 min post-dose, and at 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 h post-dose on Day 5. Blood samples were subjected to centrifugation at 2000 g for 10 min, and the respective supernatants were collected and stored at −80°C until analysis.

JMKX003142 and its metabolites (JMKX003142-M5, JMKX003142-M8-2 and JMKX003142-D4) in human plasma samples were quantified via a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Similar analytical approaches for simultaneous quantification of parent drugs and their metabolites have been previously described for kinase inhibitors,[21] and the method was validated following the bioanalytical guidelines issued by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[22] The lower limits of quantification (LLOQ) were 0.2 ng/mL for JMKX003142, 0.8 ng/mL for JMKX003142-M5, 0.3 ng/mL for JMKX003142-M8-2, and 0.2 ng/mL for JMKX003142-D4. For quality control samples of JMKX003142 and its metabolites, both intra- and inter-run accuracies (%Bias) ranged from −13.7% to 11.9%, while precisions (%CV) were within 17.9%. These results demonstrated that the LC/MS/MS method employing multiple reaction monitoring exhibited satisfactory selectivity and sensitivity for the quantification of JMKX003142 and its metabolites. Processed samples demonstrated stability at room temperature for 108 h, while reinjection reproducibility was achieved for over 100 h for all four analyses. Additionally,

long-term storage stability at −70°C was confirmed for up to 314 days, meeting the acceptance criteria with accuracy within ±15.0% and precision ≤15.0%.

The PK parameters of JMKX003142 and its metabolites following injection were calculated using non-compartmental analysis. The PK parameters in SAD study included the observed maximum concentration (C_{max}), time to C_{max} (T_{max}), area under the plasma concentration–time curve from time 0 to last quantifiable time point and time 0 to infinity (AUC_{0-t} and AUC_{0-inf}), terminal elimination half-life ($t_{1/2}$), terminal phase elimination rate constant (λ_z), clearance (CL), mean retention time from time 0 to last quantifiable time point and time 0 to infinity (MRT_{0-t} and MRT_{0-inf}), volume of distribution (V_d), and residual area percentage ($\%AUC_{ext}$). In addition to the PK parameters as outlined in the SAD study referenced above, the PK parameters of the MAD study also encompass the minimum steady state plasma concentration ($C_{min,ss}$), maximum steady-state plasma concentration ($C_{max,ss}$), average steady-state concentration ($C_{av,ss}$), time to C_{max} at steady state ($T_{max,ss}$), area under the curve during a dosing interval at steady state ($AUC_{0-\tau}$), degree of fluctuation (Fluctuation%), steady-state clearance (CL_{ss}), steady-state volume of distribution (V_{ss}), ratio of accumulation (R_{AC}). Furthermore, samples with measured concentrations below the LLOQ were defined as below limit of quantification (BLQ) and recorded as such during data acquisition. For concentration–time curves, individual or mean concentrations BLQ were plotted as missing values in semi-logarithmic plots. For individual linear plots, BLQ values before T_{max} were assigned a value of 0, whereas those observed after T_{max} were treated as missing values; measurable concentrations recorded after consecutive terminal BLQ values were retained. Mean linear curves were generated from the descriptive statistics of drug concentrations.

Pharmacodynamics Assessments

The daily cumulative urine volume, daily water intake, urinary electrolytes, and interval urine volume were recorded at baseline (Day −1), on Days 1–4 of the SAD study, and on Days 1–8 of the MAD study. Urine osmolality samples were collected at 0–72 h in the SAD study, and at 0 and 2 h on Days 1–4 as well as 0–72 h on Day 5 in the MAD study. Specifically, for SAD study, the fresh urine samples (10 mL) were collected at pre-dose (0 h) and 2, 24, 48, and 72 h post-dose and timely sent for urine osmolality detection. For MAD study, the fresh urine samples (10 mL) were collected at pre-dose (0 h) and 2 h post-dose on the Day 1 to Day 4, at pre-dose (0 h) and 2, 24, 48, and 72 h post-dose on the Day 5 and timely sent for urine osmolality detection. In SAD and MAD studies, urine samples were collected and recorded at intervals, and urine Na^+/K^+ samples were collected to detect the concentrations and excretion of urinary sodium and urinary potassium.

Urinary electrolyte excretion, urinary excretion rate, and urinary-free water clearance rate were calculated by the following formula. Urine electrolyte excretion (mEq) was calculated using the formula [urine electrolyte concentration (mEq/L) × interval urine volume (L)]. Urinary excretion rate (mL/h) was calculated as [interval urine volume (mL)/collection interval time (h)]. Urine free water clearance rate was calculated using the formula [urine excretion rate (mL/h) × [1-urinary osmotic pressure (mOsm/L)/plasma osmotic pressure (mOsm/L)]]. Among them, plasma osmotic pressure (mOsm/L) was calculated as [2 × [serum Na^+ (mmol/L) + serum K^+ (mmol/L)] + blood glucose (mg/dL)/18 + urea nitrogen (mg/dL)/2.8]; 1 mg/dL urea nitrogen was equal to 1 mmol/L urea × 2.78.

Statistical Analysis

Demographic and baseline characteristics were analyzed for subjects who were randomly enrolled and received at least one dose of study drug. Safety analyses were performed on subjects who were enrolled and received at least one dose of the study drug and had available post-drug safety data. PK and PD analyses were performed in subjects who received at least one dose of the study drug and had evaluable PK and PD data. The calculation of PK parameters was conducted utilizing Phoenix WinNonlin (version 8.3.1, Pharsight, Certara Corporation, Princeton, NJ, USA), and other statistical analyses were performed utilizing SAS software (version 9.4, SAS Institute, Inc., Cary, NC, USA). The descriptive statistics were used for the demographic characteristics, PK and PD, and safety assessments. A one-way analysis of variance (ANOVA) was employed to ascertain the statistical significance of urine volume and urinary sodium excretion between the study dose level and placebo at 4, 8 and 24 h post-dose.

Results

Demographics

A total of 78 subjects were enrolled in the study, with 48 randomized to the SAD study and 30 to the MAD study. For the SAD cohort, the median age was 32 years (range: 18–45 years), with 54.2% being male and 93.8% of Han Chinese ethnicity. The mean height, weight and BMI of SAD cohort were 167.1 cm, 65.7 kg and 23.5 kg/m^2, respectively. In the MAD cohort, the median age was 34.5 years (range: 26–41 years), with 56.7% being male and 90.0% of Han Chinese ethnicity. The mean height, weight and BMI of MAD cohort were 164.7 cm, 64.2 kg and 23.6 kg/m^2, respectively. Notably, all subjects (78/78, 100.0%) completed the intravenous injections per the study protocol and successfully finished the trial. Importantly, baseline demographic characteristics such as gender, age, height, weight, and BMI were well balanced across the SAD and MAD groups (Table 1).

Safety and Tolerability

A summary of the safety data is provided in Table 2. All TEAEs were mild, and no serious AEs (SAEs) occurred. No discontinuations, withdrawal, or deaths due to TEAEs were observed.

In the SAD study, six out of 36 subjects (16.7%) who received JMKX003142 injections developed TEAEs, and four (11.1%) experienced TRAEs. Among the 12 subjects who received placebo, nine (75%) experienced TEAEs and five (41.7%) had TRAEs. Specifically, in the placebo group, the TEAEs that occurred in ≥2 subjects included positive urine white blood cells (2 cases, 16.7%) and irregular menstruation (3 cases, 25.0%); while in the JMKX003142 group, the TEAEs that occurred in ≥2 subjects included irregular menstruation (2 cases, 5.6%). Furthermore, the only TRAE reported in ≥2 subjects in the placebo group was positive urine white blood cells (2 cases, 16.7%). Notably, no TRAEs were reported in ≥2 subjects in the JMKX003142 group.

In the MAD study, TEAEs were reported by six out of 24 subjects (25.0%) who received JMKX003142 injections, of which four (16.7%) were TRAEs. Among the six subjects who received the placebo treatment, one (16.7%) experienced TEAEs that were not related to the study treatment. In detail, one subject (16.7%) in the placebo group demonstrated elevated blood triglycerides, while TEAEs in ≥2 subjects in the JMKX003142 group included elevated blood triglycerides (2 cases, 8.3%) and elevated serum uric acid (2 cases, 8.3%). Furthermore, the only TRAE reported in ≥2 subjects in the JMKX003142 group was elevated serum uric acid, with 2 cases (8.3%), and no TRAEs were reported in the placebo group.

Overall, no significant safety risks associated with JMKX003142 injection were identified. No dose–response relationship was observed in the incidence of TEAEs.

Pharmacokinetics

In the SAD study, the mean (SD) plasma concentration–time profiles of JMKX003142 and its active metabolites (JMKX003142-M5 and JMKX003142-M8-2), and inactive metabolite (JMKX003142-D4) in linear and semi-logarithmic scale are presented in Figure 2, the PK parameters following a single dose are summarized in Tables 3 and S1. Following a single dose, JMKX003142 reached the peak concentration at the end of injection, with the T_{max} for all dose groups were 0.08 h. The $t_{1/2}$ of JMKX003142 increased slightly along with the increasing dose levels, with the mean $t_{1/2}$ ranging from 1.4 to 12.7 h. Within the dose range of 0.1 mg to 2 mg, the C_{max} of JMKX003142 increased in a generally dose-proportional manner; while the $AUC_{0\text{-inf}}$ exhibited a slight trend toward greater than dose proportionality. Within the 2 mg to 6 mg range, the plasma exposure (C_{max} and $AUC_{0\text{-inf}}$) of JMKX003142 increased in a dose-proportional manner.

In the SAD study of 0.1 mg-6 mg groups, the median T_{max} of the plasma metabolites JMKX003142-M5 and JMKX003142-M8-2 varied from 2.0 to 5.0 h, and 4.0 to 8.0 h, respectively. The mean $t_{1/2}$ of JMKX003142-M5 and JMKX003142-M8-2 varied from 14.7 to 24.3 h, and 11.1 to 15.4 h, respectively. Additionally, JMKX003142-D4 exhibited relatively low plasma concentrations, with a median T_{max} of approximately 24 h and a mean $t_{1/2}$ of approximately 56 h. In terms of molar concentration, the C_{max} of JMKX003142-M5 and JMKX003142-M8-2 represented 4.7% to 9.7% and 0.9% to 2.2% of the parent compound, respectively, while their $AUC_{0\text{-inf}}$ accounted for 166% to 233%

Table 1 Subject Demographic Characteristics

SAD study								
Characteristics	**Placebo (N = 12)**	**JMKX003142**						
		0.1 mg (N = 6)	**0.3 mg (N = 6)**	**1 mg (N = 6)**	**2 mg (N = 6)**	**4 mg (N = 6)**	**6 mg (N = 6)**	**Total (N = 48)**
Age, median (range), years	31 (21–41)	23 (21–34)	34 (24–44)	28.5 (22–43)	32.5 (22–42)	27.5 (26–43)	34.5 (18–45)	32 (18–45)
Sex, n (%)								
Male	5 (41.7)	3 (50.0)	3 (50.0)	3 (50.0)	4 (66.7)	3 (50.0)	5 (83.3)	26 (54.2)
Female	7 (58.3)	3 (50.0)	3 (50.0)	3 (50.0)	2 (33.3)	3 (50.0)	1 (16.7)	22 (45.8)
Race, n (%)								
Han	11 (91.7)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	4 (66.7)	45 (93.8)
Other	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	3 (6.3)
Height, mean (SD), (cm)	165.1 (4.4)	167.2 (12.0)	167.0 (12.4)	166.8 (4.1)	166.1 (7.8)	169.9 (3.5)	169.8 (8.9)	167.1 (7.6)
Weight, mean (SD), (kg)	67.4 (5.6)	67.0 (8.5)	69.2 (12.9)	62.9 (8.1)	61.3 (5.4)	66.6 (5.6)	64.1 (8.4)	65.7 (7.8)
BMI, mean (SD), (kg/m^2)	24.7 (1.7)	24.0 (2.1)	24.6 (2.0)	22.6 (2.9)	22.3 (2.0)	23.1 (1.6)	22.2 (1.4)	23.5 (2.1)
MAD study								
Characteristics	**Placebo (N = 6)**	**JMKX003142**						
		1 mg (N = 8)		**2 mg (N = 8)**		**4 mg (N = 8)**		**Total (N = 30)**
Age, mean (SD), years	36.5 (31–41)	29.5 (26–39)		33.5 (26–39)		37 (29–41)		34.5 (26–41)
Sex, n (%)								
Male	1 (16.7)	5 (62.5)		6 (75.0)		5 (62.5)		17 (56.7)
Female	5 (83.3)	3 (37.5)		2 (25.0)		3 (37.5)		13 (43.3)
Race, n (%)								
Han	6 (100.0)	7 (87.5)		7 (87.5)		7 (87.5)		27 (90.0%)
Other	0 (0.0)	1 (12.5)		1 (12.5)		1 (12.5)		3 (10.0%)
Height, mean (SD), (cm)	157.7 (7.5)	167.8 (7.5)		168.1 (8.0)		163.3 (6.5)		164.7 (8.13)
Weight, mean (SD), (kg)	59.7 (9.6)	66.7 (8.9)		66.3 (9.2)		63.0 (9.6)		64.2 (9.2)
BMI, mean (SD), (kg/m^2)	23.9 (2.0)	23.6 (1.8)		23.3 (1.8)		23.6 (2.8)		23.6 (2.0)

Abbreviations: SAD, single ascending doses; MAD, multiple ascending doses; SD, standard deviation; BMI, Body Mass Index.

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Table 2 Treatment-Emergent Adverse Events Following Intravenous JMKX003142

SAD study								
Parameter, n (%)	**Placebo (N = 12)**	**JMKX003142**						
		0.1 mg (N = 6)	**0.3 mg (N = 6)**	**1 mg (N = 6)**	**2 mg (N = 6)**	**4 mg (N = 6)**	**6 mg (N = 6)**	**Total (N = 48)**
Any TEAEs	9 (75.0)	0 (0.0)	2 (33.3)	2 (33.3)	0 (0.0)	1 (16.7)	1 (16.7)	15 (31.3)
Mild TEAEs	9 (75.0)	0 (0.0)	2 (33.3)	2 (33.3)	0 (0.0)	1 (16.7)	1 (16.7)	15 (31.3)
Moderate TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to treatment discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to withdrawal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs resulting in death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related AEs	5 (41.7)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	9 (18.8)
TEAEs occurring in ≥2 patients								
Irregular menstruation	3 (25.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (10.4)
Positive urinary white blood cells	2 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.3)
MAD study								
	Placebo (N = 6)	**JMKX003142**						
		1 mg (N = 8)		**2 mg (N = 8)**		**4 mg (N = 8)**		**Total (N = 30)**
Any TEAEs	1 (16.7)	3 (37.5)		2 (25.0)		1 (12.5)		7 (23.3)
Mild TEAEs	1 (16.7)	3 (37.5)		2 (25.0)		1 (12.5)		7 (23.3)
Moderate TEAEs	0 (0.0)	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)
Severe TEAEs	0 (0.0)	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)
TEAEs leading to treatment discontinuation	0 (0.0)	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)
TEAEs leading to withdrawal	0 (0.0)	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)
TEAEs resulting in death	0 (0.0)	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)
Serious AEs	0 (0.0)	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)
Treatment-related AEs	0 (0.0)	2 (25.0)		2 (25.0)		0 (0.0)		4 (13.3)
TEAEs occurring in ≥2 patients								
Elevated blood triglycerides	1 (16.7)	1 (12.5)		0 (0.0)		1 (12.5)		3 (10.0)
Elevated blood uric acid	0 (0.0)	0 (0.0)		2 (25.0)		0 (0.0)		2 (6.7)

Abbreviations: SAD, single ascending doses; MAD, multiple ascending doses; AEs, adverse events; TEAEs, Treatment-emergent adverse events.

and 15.4% to 58.3% of the parent compound. Moreover, JMKX003142-D4 had a C_{max} accounted for 0.2% to 0.4% of the parent compound, with an $AUC_{0\text{-inf}}$ accounting for 20.5% of the parent compound. Across the 0.1 mg to 6 mg dosing range, the increases in plasma exposure (C_{max} and $AUC_{0\text{-inf}}$) of JMKX003142-M5 and JMKX003142-M8-2 were higher than dose-proportional.

In the MAD study, the mean (SD) plasma concentration–time profiles of JMKX003142, its active metabolites (JMKX003142-M5 and JMKX003142-M8-2) and inactive metabolite (JMKX003142-D4) in linear and semi-logarithmic scale are presented in Figure 3, the PK parameters on both Day 1 and Day 5 are summarized in Tables 4 and S1. After continuous administration for 5 days, JMKX003142 reached peak plasma concentration at the end of intravenous injection on Day 5, with a median $T_{max,ss}$ of 0.03 h across all groups. On Day 5, the mean $C_{max,ss}$ for the 1 mg, 2 mg, and 4 mg groups were 69.7 ng/mL, 128 ng/mL, and 312 ng/mL, respectively, which were comparable to C_{max} values on Day 1 at the same doses (1 mg: 58.1 ng/mL; 2 mg: 96.9 ng/mL; 4 mg: 289 ng/mL). The mean $t_{1/2}$ of the 1 mg, 2 mg and 4 mg groups was 11.1 h, 11.8 h and 11.1 h, respectively, while the mean $AUC_{0\text{-}\tau}$ was 31.3 h*ng/mL, 72.6 h*ng/mL and 152 h*ng/mL, respectively. The $C_{max,ss}$ of JMKX003142 increased in a generally dose-proportional manner, whereas the increase in

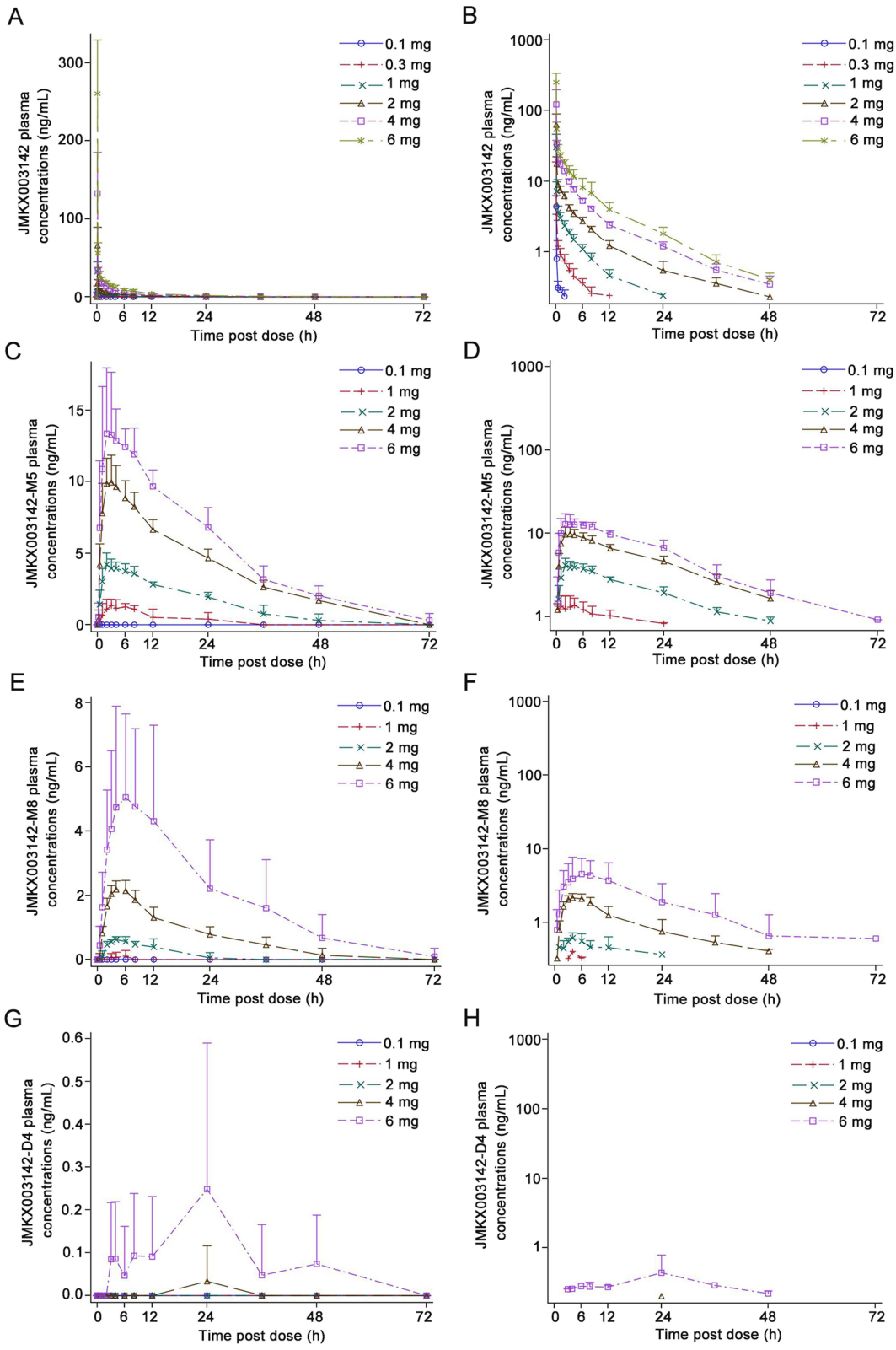

Figure 2 JMKX003142 and metabolite mean plasma concentrations after single dose administration. (**A** and **B**) Mean (SD) JMKX003142 plasma concentration vs time profiles following single dose in healthy adult participants on linear (**A**) and Semi-logarithmic scale (**B**). (**C** and **D**) Mean (SD) JMKX003142-M5 plasma concentration vs time profiles following single dose in healthy adult participants on linear (**C**) and Semi-logarithmic scale (**D**). (**E** and **F**) Mean (SD) JMKX003142-M8-2 plasma concentration vs time profiles following single dose in healthy adult participants on linear (**E**) and Semi-logarithmic scale (**F**). (**G** and **H**) Mean (SD) JMKX003142-D4 plasma concentration vs time profiles following single dose in healthy adult participants on linear (**G**) and Semi-logarithmic scale (**H**).

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Table 3 Pharmacokinetic Parameters for JMKX003142 and Its Metabolites After Single Ascending Doses of JMKX003142

JMKX003142						
Parameter	**0.1 mg (N = 6)**	**0.3 mg (N = 6)**	**1 mg (N = 6)**	**2 mg (N = 6)**	**4 mg (N = 6)**	**6 mg (N = 6)**
T_{max} (h)[a]	0.08 (0.08, 0.2)	0.08 (0.08, 0.17)	0.08 (0.08, 0.08)	0.08 (0.08, 0.08)	0.08 (0.08, 0.08)	0.08 (0.08, 0.08)
C_{max} (ng/mL)	4.7 (1.6)	8.8 (4.7)	32.7 (12.4)	66.3 (22.9)	133 (52.7)	261 (68.9)
AUC_{0-t} (h*ng/mL)	0.9 (0.5)	4.9 (1.6)	20.6 (3.8)	61.9 (9.8)	137 (10.7)	212 (29.5)
AUC_{0-inf} (h*ng/mL)	1.4 (1.1)	6.4 (1.8)	23.5 (4.1)	67.0 (10.6)	144 (12.5)	218 (30.1)
$t_{1/2}$ (h)	1.4 (1.7)	3.5 (1.9)	5.2 (1.6)	10.0 (3.9)	12.7 (2.1)	10.4 (0.9)
λ_z (1/h)	1.6 (1.7)	0.2 (0.09)	0.1 (0.03)	0.08 (0.03)	0.06 (0.009)	0.07 (0.006)
CL (L/h)	109 (70.2)	50.6 (17.4)	43.8 (8.8)	30.5 (5.0)	28.0 (2.8)	28.0 (4.0)
V_d (L)	107 (59.0)	234 (89.0)	320 (68.8)	422 (111)	508 (66.5)	421 (76.0)
JMKX003142-M5						
Parameter	**0.1 mg (N = 6)**	**0.3 mg (N = 6)**	**1 mg (N = 6)**	**2 mg (N = 6)**	**4 mg (N = 6)**	**6 mg (N = 6)**
T_{max} (h)[a]	–	–	4.5 (2.0, 6.0)	2.0 (2.0, 4.0)	3.0 (2.0, 4.0)	5.0 (1.0, 8.0)
C_{max} (ng/mL)	–	–	1.4 (0.4)	4.3 (0.7)	10.6 (2.0)	14.6 (4.2)
AUC_{0-t} (h*ng/mL)	–	–	16.6 (10.2)	85.6 (18.2)	233 (27.6)	336 (49.5)
AUC_{0-inf} (h*ng/mL)	–	–	50.8 (21.3)	115 (14.9)	275 (34.7)	365 (46.4)
$t_{1/2}$ (h)	–	–	24.3 (14.9)	17.8 (3.7)	17.0 (3.0)	14.7 (2.7)
λ_z (1/h)	–	–	0.04 (0.03)	0.04 (0.009)	0.04 (0.008)	0.05 (0.009)
CL (L/h)	–	–	25.0 (17.0)	17.6 (2.2)	14.7 (1.9)	16.7 (2.2)
V_d (L)	–	–	663 (155)	445 (73.4)	358 (66.2)	348 (43.6)
JMKX003142-M8-2						
Parameter	**0.1 mg (N = 6)**	**0.3 mg (N = 6)**	**1 mg (N = 6)**	**2 mg (N = 6)**	**4 mg (N = 6)**	**6 mg (N = 6)**
T_{max} (h)[a]	–	–	4.0 (3.0, 6.0)	6.0 (3.0, 12.0)	4.0 (3.0, 6.0)	8.0 (4.0,12.0)
C_{max} (ng/mL)	–	–	0.4 (0.04)	0.7 (0.06)	2.3 (0.3)	5.5 (2.8)
AUC_{0-t} (h*ng/mL)	–	–	0.5 (0.4)	6.23 (3.3)	40.5 (6.1)	126 (93.8)
AUC_{0-inf} (h*ng/mL)	–	–	–	11.7 (1.5)	52.2 (7.5)	138 (93.0)
$t_{1/2}$ (h)	–	–	–	11.1 (1.3)	15.4 (3.4)	14.7 (5.3)
λ_z (1/h)	–	–	–	0.06 (0.008)	0.05 (0.01)	0.05 (0.01)
CL (L/h)	–	–	–	173 (23.8)	78.2 (12.6)	54.2 (20.4)
V_d (L)	–	–	–	2770.0 (545.0)	1690.0 (217.0)	1230.0 (834.0)

Note: [a] Data are expressed as mean ± standard deviation, except T_{max} which is the median (range).

Abbreviations: T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration; $t_{1/2}$, terminal half-life; AUC, area under the plasma concentration–time curve; AUC_{0-t}, AUC from time 0 to last quantifiable timepoint; AUC_{0-inf}, AUC from time 0 to infinity; λ_z, Terminal Phase Elimination Rate Constant; CL, renal clearance; V_d Apparent Volume of Distribution.

$AUC_{0-\tau}$ was slightly higher than dose-proportional. Notably, the accumulation ratio Rac[C_{max}] and Rac[$AUC_{0-\tau}$] were 1.2 to 1.8 and 1.2, respectively, demonstrating negligible plasma accumulation of JMKX003142 after multiple doses.

Following multiple doses, the median $T_{max,ss}$ of metabolites JMKX003142-M5 and JMKX003142-M8-2 within the dose range of 1 mg to 4 mg were 1.5 h to 2.0 h and 3.5 h to 5.0 h, respectively. The mean $t_{1/2}$ of JMKX003142-M5 and JMKX003142-M8-2 within the dose range of 1 mg to 4 mg was 15.7 h to 19.9 h and 9.6 h to 17.4 h, respectively. Moreover, the plasma concentration of JMKX003142-D4 was relatively low, with a median $T_{max,ss}$ ranging from approximately 3.0 h to 13.5 h and a mean $t_{1/2}$ of 113 h. Based on the molar concentration, the $C_{max,ss}$ of the metabolites JMKX003142-M5, JMKX003142-M8-2, and JMKX003142-D4 after multiple doses accounted for 5.42% to 6.42%, 0.614% to 1.23%, and 0.259% to 0.272% of the parent compound, respectively. Correspondingly, their $AUC_{0-\tau}$represented 161% to 183%, 3.47% to 34.3%, and 1.68% to 8.63% of the parent compound, respectively. Within the dose range of 1 mg to 4 mg, the $C_{max,ss}$ of JMKX003142-M5 increased slightly beyond dose-proportional, while $AUC_{0-\tau}$ generally increased in a dose-proportional manner. However, the increase in exposure ($C_{max,ss}$ and $AUC_{0-\tau}$) of JMKX003142-M8-2 increased higher than dose-proportional. Furthermore, following repeated doses, a slight

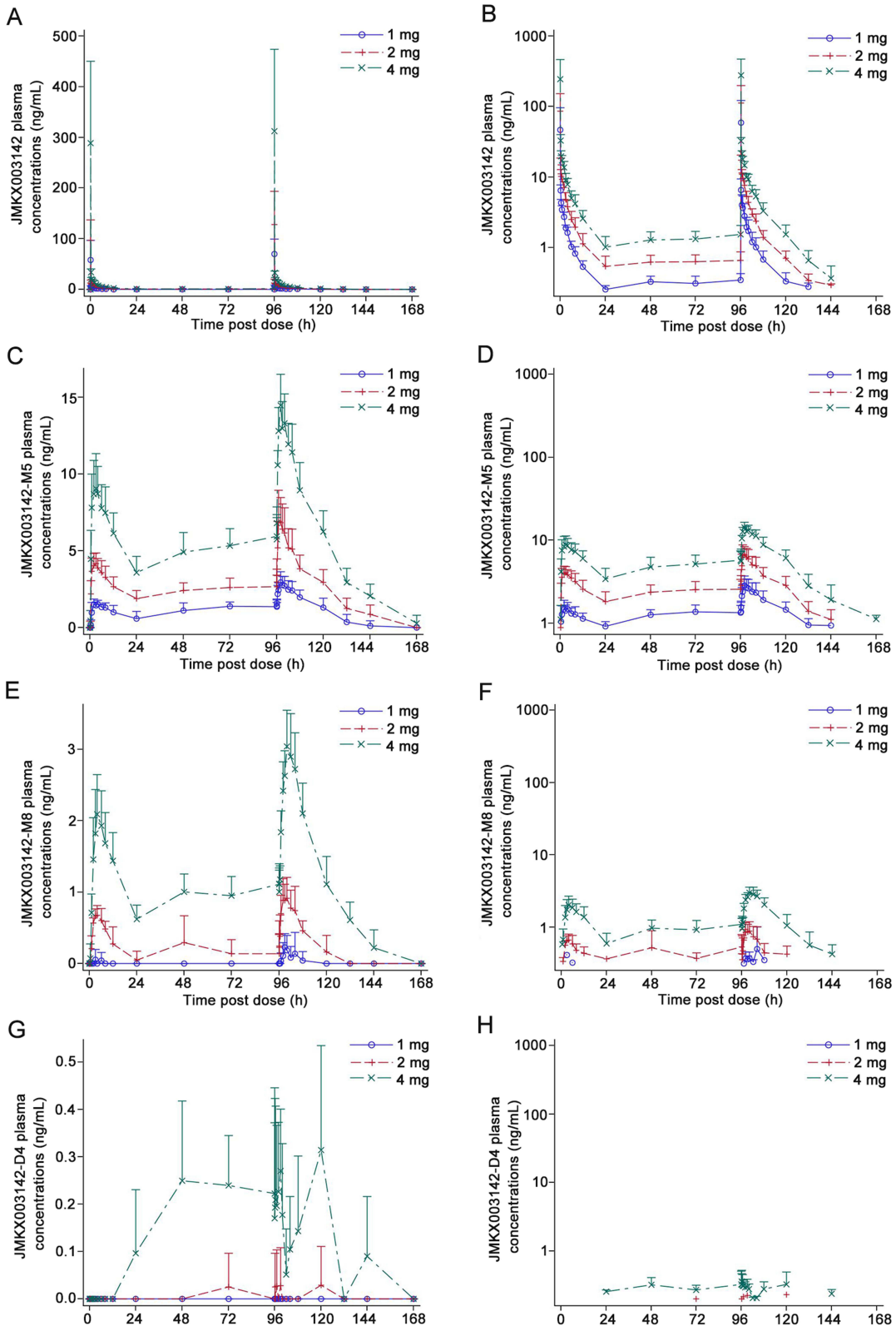

Figure 3 JMKX003142 and metabolite mean plasma concentrations after multiple dose administration. (**A** and **B**) Mean (SD) JMKX003142 plasma concentration vs time profiles following multiple doses in healthy adult participants on linear (**A**) and Semi-logarithmic scale (**B**). (**C** and **D**) Mean (SD) JMKX003142-M5 plasma concentration vs time profiles following multiple doses in healthy adult participants on linear (**C**) and Semi-logarithmic scale (**D**); (**E** and **F**) Mean (SD) JMKX003142-M8-2 plasma concentration vs time profiles following multiple doses in healthy adult participants on linear (**E**) and Semi-logarithmic scale (**F**). (**G** and **H**) Mean (SD) JMKX003142-D4 plasma concentration vs time profiles following multiple doses in healthy adult participants on linear (**G**) and Semi-logarithmic scale (**H**).

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Table 4 Pharmacokinetic Parameters for JMKX003142 and Its Metabolites After Multiple Ascending Doses of JMKX003142

JMKX003142	**Day 1**			**Day 5**		
Parameter	**1 mg (N = 8)**	**2 mg (N = 8)**	**4 mg (N = 8)**	**1 mg (N = 8)**	**2 mg (N = 8)**	**4 mg (N = 8)**
T_{max} (h)[a]	0.03 (0.03, 0.03)	0.03 (0.03, 0.05)	0.03 (0.03, 0.03)	–	–	–
C_{max} (ng/mL)	58.1 (39.0)	96.9 (40.5)	289.0 (161.0)	–	–	–
AUC_{0-t} (h*ng/mL)	26.4 (4.7)	62.6 (14.0)	131 (21.1)	32.4 (10.2)	79.3 (14.6)	171 (20.7)
AUC_{0-inf} (h*ng/mL)	29.8 (5.35)	69.6 (16.3)	143 (24.6)	37.1 (11.0)	84.8 (14.5)	178 (20.8)
$T_{max,ss}$ (h) [a]	–	–	–	0.03 (0.03, 0.03)	0.03 (0.03, 0.05)	0.03 (0.03,0.03)
$C_{max,ss}$ (ng/mL)	–	–	–	69.7 (29.8)	128 (65.4)	312 (162)
$C_{min,ss}$ (ng/mL)	–	–	–	0.3 (0.09)	0.7 (0.2)	1.5 (0.5)
$AUC_{0-\tau}$	–	–	–	31.3 (8.6)	72.6 (11.7)	152 (16.6)
Rac_C_{max}	–	–	–	1.8 (1.4)	1.4 (0.5)	1.2 (0.3)
Rac_AUC	–	–	–	1.2 (0.3)	1.2 (0.1)	1.2 (0.2)
Fluctuation%	–	–	–	5060 (1600)	4180 (1950)	4960 (2670)
JMKX003142-M5	**Day 1**			**Day 5**		
Parameter	**1 mg (N = 8)**	**2 mg (N = 8)**	**4 mg (N = 8)**	**1 mg (N = 8)**	**2 mg (N = 8)**	**4 mg (N = 8)**
T_{max} (h)[a]	2.5 (2.0, 8.0)	2.5 (1.0, 4.0)	2.5 (1.0, 4.0)	–	–	–
C_{max} (ng/mL)	1.7 (0.3)	4.3 (0.7)	9.7 (2.3)	–	–	–
AUC_{0-t} (h*ng/mL)	22.1 (9.2)	66.3 (14.1)	145 (27.4)	55.3 (24.0)	139 (41.7)	324 (63.1)
AUC_{0-inf} (h*ng/mL)	56.7 (20.2)	119 (35.6)	230 (60.9)	87.8 (20.8)	171 (44.1)	359 (70.7)
$T_{max,ss}$ (h) [a]	–	–	–	2.0 (2.0, 3.0)	1.5 (1.0, 2.0)	2.0 (2.0, 4.0)
$C_{max,ss}$ (ng/mL)	–	–	–	2.9 (0.6)	7.1 (1.9)	14.6 (2.0)
$C_{min,ss}$ (ng/mL)	–	–	–	1.3 (0.3)	2.6 (0.7)	5.6 (1.3)
$AUC_{0-\tau}$	–	–	–	49.2 (11.3)	104 (25.4)	230 (33.9)
Rac_C_{max}	–	–	–	1.8 (0.4)	1.6 (0.2)	1.6 (0.3)
Rac_AUC	–	–	–	1.9 (0.5)	1.6 (0.2)	1.6 (0.3)
Fluctuation%	–	–	–	75.6 (15.7)	96.3 (27.4)	88.6 (25.5)
JMKX003142-M8-2	**Day 1**			**Day 5**		
Parameter	**1 mg (N = 8)**	**2 mg (N = 8)**	**4 mg (N = 8)**	**1 mg (N = 8)**	**2 mg (N = 8)**	**4 mg (N = 8)**
T_{max} (h)[a]	4.5 (3.0, 6.0)	3.5 (2.0, 6.0)	4.0 (3.0, 8.0)	–	–	–
C_{max} (ng/mL)	0.4 (0.06)	0.7 (0.1)	2.2 (0.6)	–	–	–
AUC_{0-t} (h*ng/mL)	0.3 (0.08)	5.9 (3.0)	30.1 (6.8)	1.2 (0.8)	10.8 (6.0)	61.6 (11.3)
AUC_{0-inf} (h*ng/mL)	–	15.2 (7.9)	41.0 (10.0)	6.7 (2.2)	17.2 (8.4)	73.9 (12.5)
$T_{max,ss}$ (h) [a]	–	–	–	5.0 (2.0, 12.0)	3.5 (3.0, 8.0)	5.0 (2.0, 8.0)
$C_{max,ss}$ (ng/mL)	–	–	–	0.5 (0.2)	1.0 (0.3)	3.2 (0.5)
$C_{min,ss}$ (ng/mL)	–	–	–	0 (0)	0.09 (0.2)	0.9 (0.3)
$AUC_{0-\tau}$	–	–	–	5.2 (0.7)	12.6 (4.8)	48.5 (8.0)
Rac_C_{max}	–	–	–	1.6 (0.5)	1.3 (0.3)	1.5 (0.3)
Rac_AUC	–	–	–	–	1.4 (0.4)	1.7 (0.3)
Fluctuation%	–	–	–	174 (69.4)	143 (41.7)	103 (27.4)

Notes: [a]Data are expressed as mean ± standard deviation, except T_{max} which is the median (range).

Abbrevaitions: T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration; $t_{1/2}$, terminal half-life; AUC, area under the plasma concentration–time curve; AUC_{0-t}, AUC from time 0 to last quantifiable timepoint; AUC_{0-inf}, AUC from time 0 to infinity; Rac, ratio of accumulation.

accumulation of metabolites was observed in the plasma. Specifically, the accumulation ratio (Rac[C_{max}]) was 1.6–1.8 for JMKX003142-M5, 1.3–1.6 for JMKX003142-M8-2, and 1.9 for JMKX003142-D4. Correspondingly, the Rac[$AUC_{0-\tau}$] ranged from 1.6 to 1.9 for JMKX003142-M5 and from 1.4 to 1.7 for JMKX003142-M8-2, respectively. Overall, the variability of exposure and PK parameters was minimal for JMKX003142 and its metabolites.

Pharmacodynamics

Following a single dose, the changes in daily cumulative urine volume and daily fluid intake from baseline to 24 h post-dose were greater in the 1 mg and higher dose group than in the placebo group. Furthermore, the daily cumulative urine volume, daily fluid intake, and their changes from baseline exhibited a significant dose-dependent correlation, with values increasing in tandem with escalating doses (Figure 4A and B). Notably, the cumulative urine volume in the 2–6 mg dose group was significantly higher than that in the placebo group at 24 h post-dose ($P<0.001$), while there was no significant difference in urinary sodium excretion (Figure 4C and D). Moreover, the analysis of urinary excretion rate indicated that the predominant change in urine volume occurred within the 0–12 h interval, with a more pronounced occurrence within the 0–2 h and 4–8 h periods (Figure S1). After a single dose, the urinary free water clearance rate in the JMKX003142 group was significantly higher than that in the placebo group during the 2–12 h period (Figure S2). In the ≥0.3 mg dose groups, the concentrations of urinary sodium and potassium decreased within 0–4 h, subsequently increased, and returned to baseline levels by 72 h (Figures S3 and S4). Similarly, the transient increases in urinary sodium and potassium excretion normalized within 2–3 days (Figure S5). For all dose groups, the urine osmotic pressure was significantly lower than that of the placebo group at 2 h post-dose then increased significantly within 24 to 72 h and eventually returned to the baseline levels (Figure S6).

Following multiple doses, the daily cumulative urine volume, daily fluid intake, and their changes from baseline were significantly higher than those in the placebo group, with values elevating in tandem with the dose escalation (Figure 4E and F). Of note, after 5 days of continuous administration, the 24 h cumulative urine volume in each dose group was significantly higher than that in the placebo group ($P<0.05$), while no significant difference was observed in urinary sodium excretion between groups (Figure 4G and H). After multiple doses, the mean urinary excretion rate of the 2 mg and 4 mg groups exceeded that of the placebo group at all-time points, with a particularly significant change in urine volume observed between 4–8 h (Figure S1). Urinary free water clearance also increased dose-dependently versus placebo (Figure S2). Urinary sodium and potassium concentrations decreased within 4 h post-dose, subsequently increased, and stabilized by 48h (Figures S3 and S4). After 5 days of dosing, sodium and potassium excretion were increased compared with baseline but remained below the levels recorded on Day 1 (Figure S5). Daily injections resulted in significant reductions in urine osmotic pressure, which recovered prior to the next injection and returned to baseline levels (Figure S6).

To conclude, JMKX003142 injection exhibited favourable PD outcomes. The alterations in the free water clearance rate and urine osmotic pressure were consistent with the JMKX003142's capacity to facilitate the excretion of electrolyte-free water from the body.

Exposure–Response Relationship

The PK-PD time-course profile following a single dose is presented in Figure S7. The relationship of exposure vs urinary excretion rate is presented in Figure S8. Our analysis revealed a correlation between the exposure levels of JMKX003142-M5 and a pronounced increase in urine volume during the 4–8 h period following injection.

Discussion

This randomized, double-blind, placebo-controlled, dose-escalation Phase I clinical trial represents the first-in-human investigation of JMKX003142 injection, designed to comprehensively evaluate its safety, tolerability, PK and PD profiles in healthy adult subjects following single dose and multiple doses. Our findings revealed that JMKX003142 injection was safe and well tolerated in healthy subjects. Within the dose range of this study, JMKX003142 reached the peak concentration at the end of injection, with C_{max} exhibiting a general dose-proportional increase. Furthermore, JMKX003142 injection demonstrated favourable diuretic properties versus placebo, characterized by elevated daily urine volume and fluid intake within 24 h post-dose. It is important to note that these findings were obtained in a healthy volunteer population, laying a necessary foundation for clinical development. An ongoing Phase II study (CTR20251510) is underway to evaluate the efficacy and safety of JMKX003142 injection in patients with HF.

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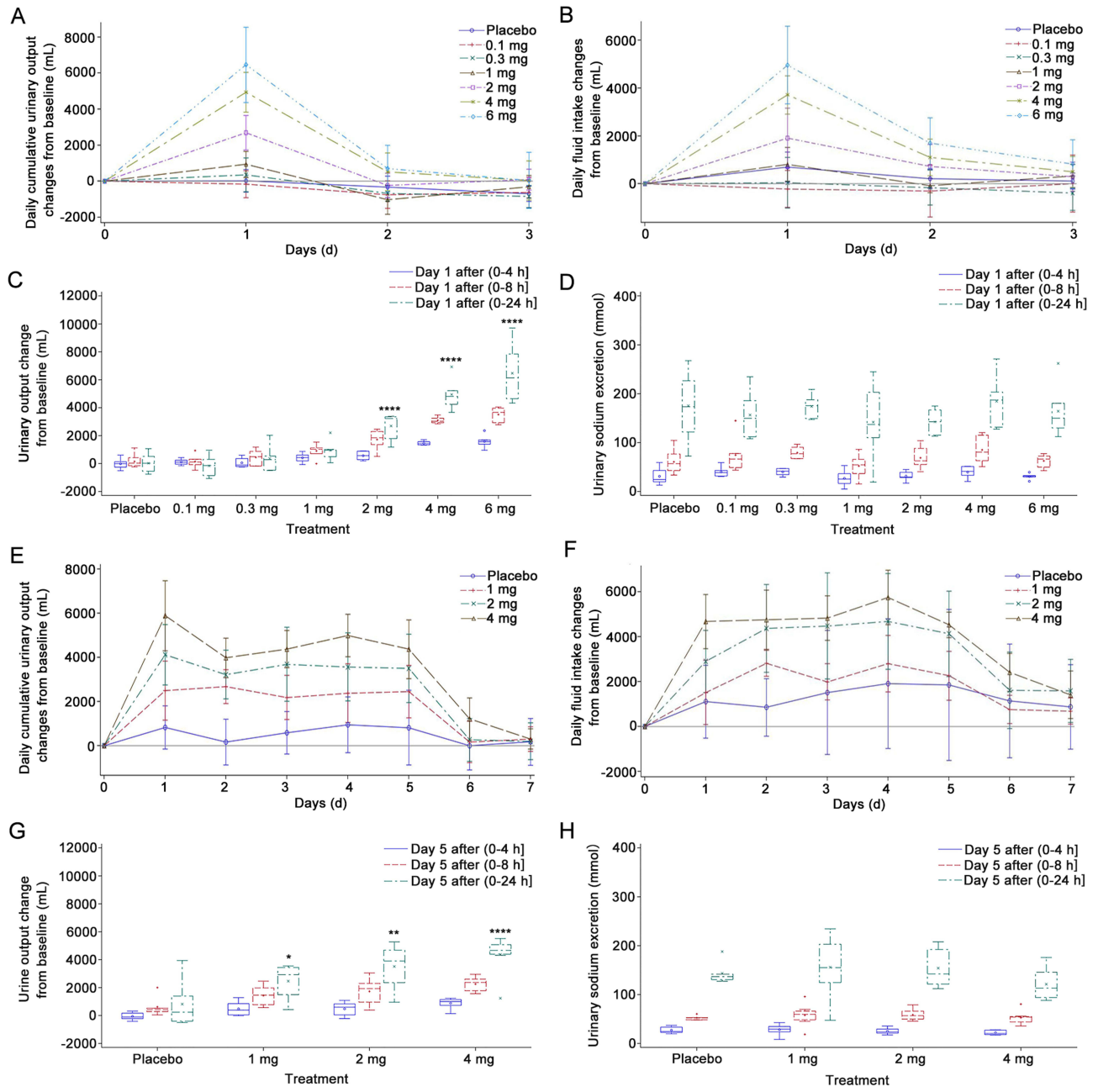

Figure 4 The changes in urinary volume, fluid intake, and urinary sodium excretion from baseline following a single and multiple doses of JMKX003142 or placebo in Chinese healthy subjects. (**A**) Mean (SD) changes in daily cumulative urine volume from baseline following a single dose of JMKX003142 injection or placebo. (**B**) Mean (SD) changes in daily fluid intake from baseline following a single dose of JMKX003142 injection or placebo. (**C**) Baseline-adjusted urine volume following a single dose of JMKX003142 or placebo in healthy subjects. Each boxplot illustrates the distribution of baseline-adjusted urine volume over 4-, 8-, and 24 h post-dose; ANOVA was performed between dose levels and placebo to assess statistically significant mean differences, **** represents P-value <0.0001. (**D**) Baseline-adjusted urinary sodium excretion following a single dose of JMKX003142 or placebo in healthy subjects. Each boxplot illustrates the distribution of baseline-adjusted urinary sodium excretion over 4-, 8-, and 24-hour post-dose; ANOVA was performed between dose levels and placebo to assess statistically significant mean differences. (**E**) Mean (SD) changes in daily cumulative urine volume from baseline following multiple doses of JMKX003142 injection or placebo. (**F**) Mean (SD) changes in daily fluid intake from baseline following multiple doses of JMKX003142 injection or placebo. (**G**) Baseline-adjusted urine volume following multiple doses of JMKX003142 or placebo in healthy subjects. Each boxplot illustrates the distribution of baseline-adjusted urine volume over 4-, 8-, and 24-hour post-dose; ANOVA was performed between dose levels and placebo to assess statistically significant mean differences, *represents P-value <0.05, **represents P-value <0.01, **** represents P-value <0.0001. (**H**) Baseline-adjusted urinary sodium excretion following multiple doses of JMKX003142 or placebo in healthy subjects. Each boxplot illustrates the distribution of baseline-adjusted urinary sodium excretion over 4-, 8-, and 24-hour post-dose; ANOVA was performed between dose levels and placebo to assess statistically significant mean differences.

All reported TEAEs were mild, with no deaths, SAEs, or discontinuations due to TEAEs occurred. The most prevalent TRAEs of JMKX003142 injection in healthy adult subjects were elevated serum uric acid. Consistently, the elevated serum uric acid also occurred following oral or intravenous administration of tolvaptan, a drug targeting the same receptor.[4,23,24] Previous studies have shown that tolvaptan inhibits the urine concentration activity mediated by the antidiuretic V_2 receptor. This inhibition may have led to an increase in blood uric acid levels by significantly reducing the excretion of solute water and the glomerular filtration rate.[24,25] In this study, all subjects with elevated serum uric acid returned to normal without intervention, with short AE durations and no gout attacks reported in any subject. Other occasional TEAEs in JMKX003142 group, such as positive urine white blood cell count, and elevated blood triglycerides similar to reports of tolvaptan.[26–28] Furthermore, injection-related AEs associated with tolvaptan phosphate sodium have been documented, including erythema, pruritus, and paresthesia. These AEs are not attributable to the pharmacological effects of tolvaptan itself, but rather to venous endothelial and nerve ending stimulation by sodium phosphate at high infusion rates, and their incidence can be reduced by lowering the infusion speed.[18] Importantly, no injection-related AEs were observed in this study despite the rapid intravenous administration of JMKX003142 (5 min for SAD; 2 min for MAD), supporting the feasibility of rapid intravenous dosing for JMKX003142 injection. Unexpectedly, the incidence of TEAEs was remarkably higher in the placebo group than in the JMKX003142 group in the SAD study (75.0% vs 31.3%), likely due to the smaller placebo group sample size (n = 12 vs n = 36), which may overestimate sporadic events. Meanwhile, the incidence of TEAEs in the placebo group was lower than that in the JMKX003142 group in the MAD study, further indicating that the high TEAE incidence observed in the placebo group of the SAD study was not a universal finding. Moreover, the most common TEAEs in the placebo group (positive urinary white blood cells, irregular menstruation) were also observed in the JMKX003142 group. In addition, the proportion of female subjects was higher in the placebo group, indicating that such TEAEs are more likely related to physiological fluctuations in healthy subjects or sampling-related artifacts.

Following single and multiple injections, plasma concentrations of JMKX003142 and its metabolites increased with dose level. Furthermore, the plasma drug concentrations of each dose group showed similar trends over time. In both SAD and MAD studies, JMKX003142 reached peak plasma concentration after the end of administration, indicating the rapid onset characteristic of JMKX003142 injection. It is noteworthy that the median T_{max} of JMKX003142 in the SAD study (0.08 h) was marginally later than that in the MAD study (0.03 h), likely attributable to the differing administration durations of (5 min vs 2 min). Importantly, JMKX003142 not only shortened the infusion duration without significantly increasing injection-related AEs but also accelerated T_{max}, which may rapidly alleviate acute volume overload symptoms and thus greatly optimize the treatment of acute HF. Moreover, our findings indicated that the C_{max} of JMKX003142 injection increased essentially in a dose-proportional manner, indicating no absorption saturation within the study dose range. This contrasts with tolvaptan, whose C_{max} increases were non-dose-proportional, potentially due to saturated absorption in the upper small intestine at higher doses.[29] Nevertheless, following a single injection of JMKX003142 over the 0.1–2 mg dose range, AUC increased in a greater than dose-proportional manner, a phenomenon mainly attributed to distribution-phase kinetics at low doses. Within this range, early plasma concentrations fell rapidly below the LLOQ, resulting in >20% extrapolation for $AUC_{0\text{-inf}}$, and consequent underestimation of AUC and overestimation of CL. Thus, the apparent supra-proportional exposure does not accurately characterize the elimination phase.[30–32] Notably, AUC increased in a dose-proportional manner across the 2–6 mg range, suggesting no apparent saturation in absorption, distribution, or elimination processes. For drug development, this predictable exposure within the 2–6 mg range mitigates the risk of abrupt toxicity increases associated with nonlinear accumulation. As expected, negligible plasma accumulation was observed following multiple injections, further indicating well-controlled steady-state exposure and a low risk of accumulation-related toxicity. Moreover, the stable $t_{1/2}$ (10–12.7 h) observed across 2–6 mg dose range contributes to consistent exposure, supporting a clinically favorable once-daily dosing and thereby improving patient compliance. Collectively, the stable and predictable PK profile within the 2–6 mg dose range identifies it as a pivotal dose range for subsequent clinical development, while providing critical support for dosing interval determination, accumulation risk assessment, and exposure-response analyses.

This study also evaluated the PK characteristics of JMKX003142 metabolites. Five metabolites were detected in plasma, with active metabolite JMKX003142-M5 demonstrating the highest activity and exposure, suggesting its role as

the primary active component after the metabolism of JMKX003142. Notably, JMKX003142-M5 exhibited higher exposure and a longer $t_{1/2}$ compared to the parent drug JMKX003142, which supports a sustained therapeutic effect. This PK profile allows for a reduced dosing frequency, thereby improving patient compliance. Furthermore, JMKX003142-M5 exhibited only slight accumulation after multiple injections, with an accumulation ratio of less than 2. This finding demonstrates moderate and predictable increases in exposure with repeated dosing, without disproportionate accumulation beyond physiological tolerance, thus supporting the safety of the current dosing regimen.

JMKX003142 injection has demonstrated favourable PD profiles, including enhanced daily cumulative urine volume, daily fluid intake, interval urine volume, urine excretion rate, urine free water clearance rate, urine electrolytes, and urine osmotic pressure. In 1 mg or higher dose group, the 24 h post-dose daily cumulative urine volume, daily fluid intake, and their changes from baseline were higher than in the placebo group, with a dose-dependent increasing trend. While no published urine volume data exist for tolvaptan sodium phosphate in healthy subjects, the PK outcomes of tolvaptan tablets in healthy subjects suggest that once-daily oral administration of tolvaptan tablets 15 mg is equivalent to once-daily intravenous injection of tolvaptan sodium phosphate 16 mg.[4,29] Therefore, an indirect comparison of the urine volume can be made between JMKX003142 injection and tolvaptan tablets. Previous studies reported 24 h urine volume of 3018.5 ± 729.9 mL with 15 mg oral tolvaptan versus 2584.5 ± 1298.4 mL with placebo.[29] Similarly, in this study, the urine volume after a single injection of JMKX003142 injection 1 mg was 3739.0 ± 901.46 mL, while the urine volume of placebo group was 3164.7 ± 1019.92 mL. Beyond similar diuretic effects at doses of 1 mg or higher, the intravenous formulation of JMKX003142 confers unique clinical benefits. Specifically, compared with oral tolvaptan, its intravenous administration enables reliable, precise, and rapid drug delivery. This feature is essential for emergency scenarios where oral intake is unfeasible (eg, acute nausea/vomiting, perioperative fasting, or enteral nutrition restriction) or rapid onset is mandatory. Thus, JMKX003142 injection represents a pivotal therapeutic option for this specific patient population with unmet clinical needs.

The analysis of urinary excretion rate revealed that the increase in urine volume within 12 h post-dose urine volume increases were significantly higher in JMKX003142 groups than in the placebo group, with the most marked elevations observed at 0–2 h and 4–8 h post-dose. The PK data demonstrated that JMKX003142 reached peak concentration at the end of administration, while the active metabolite JMKX003142-M5 peaked at 2–5 h post-dose. Notably, the plasma exposure (AUC) of JMKX003142-M5 was higher than that of JMKX003142. Therefore, we speculated that the significant increase in urine volume at 0–2 h and 4–8 h post-dose is likely attribute to the diuretic effect of JMKX003142 and JMKX003142-M5. By comparison, a Phase III trial conducted in congestive HF patients with oral intake difficulties demonstrated that intravenous tolvaptan sodium phosphate induced significant urine volume within 0–1 h post-first dose, peaked at 1–2 h, and generally returned to the baseline by 4–6 h post-dose.[33] The relationship between drug exposure and urinary excretion rate also revealed a correlation between the exposure of JMKX003142-M5 and the significant increase in urine volume at 4–8 h post-dose (Figure S8). The above results indicated that the diuretic effect of JMKX003142 is more persistent due to the active metabolites. It is noteworthy that no significant increase in urine volume was observed compared to placebo over a 12 h period, indicating that JMKX003142 did not significantly increase enuresis nocturna. Furthermore, changes in free water clearance rate and urine osmotic pressure are consistent with the pharmacological mechanism of JMKX003142 in promoting the excretion of electrolyte-free water.

The safety, PK, and PD profile from this study provide a critical basis for Phase II dose selection of JMKX003142 in patients with fluid retention due to HF. The PK profile demonstrates that the rapid onset of JMKX003142 and the long-acting activity of JMKX003142-M5 act synergistically to achieve both prompt symptom control and sustained therapeutic maintenance. Notably, negligible accumulation of the parent drug and minimal accumulation of the active metabolite (JMKX003142-M5) were observed with repeated dosing, indicating a low risk of accumulation-related toxicity. Additionally, the $t_{1/2}$ supports once-daily dosing, and the intravenous formulation's rapid peak attainment justifies its use for prompt diuresis in HF. The PD data demonstrate that repeated JMKX003142 injections (≥1 mg) exert pronounced, sustained diuretic effects, establishing the minimum effective dose for Phase II studies. Integrating the safety data, daily intravenous JMKX003142 at 1 mg to 4 mg is expected to achieve an optimal diuretic response.

The strengths of the study include a conventional dose escalation design and stringent dose escalation rules to control potential safety risks. Furthermore, the study incorporated numerous dose cohorts with placebo controls, employing

randomization and blinded treatments to minimize the assessment bias. However, a limitation of the study lays in the limited participant numbers in each dose group may result in restriction of statistical analysis; for instance, the small sample size of the placebo group contributed to its relatively high incidence of TEAEs in the SAD study. Despite this inherent limitation, as a phase I study primarily designed to investigate the tolerated dose in humans, the trial has comprehensively characterized the PK and PD profiles of JMKX003142 injection and provided an initial evaluation of its safety. The overall findings furnish substantial evidence supporting further Phase II evaluation in patients with HF. Furthermore, as a V2R antagonist, the rapid and short-term diuretic effects of JMKX003142 injection also define a clear development pathway for treating acute fluid and sodium retention disorders. Future clinical studies will extend beyond HF-associated fluid retention to systematically evaluate the therapeutic value of JMKX003142 injection in hyponatremia, fluid and sodium retention caused by renal failure, and the syndrome of inappropriate antidiuretic hormone secretion.

Conclusions

JMKX003142 injection constitutes a new intravenous formulation of AVP V2R antagonists. In this first-in-human study, JMKX003142 injection demonstrated favourable safety, tolerability, PK, and PD profiles in healthy subjects after single and multiple doses. JMKX003142 injection has the potential to be an effective intravenous preparation for the treatment of fluid retention caused by HF.

Data Sharing Statement

De-identified individual participant data that support the finding of this study are available from the corresponding author (Haiyan Li; E-mail:haiyanli1027@hotmail.com; haiyanli_bysy@bjmu.edu.cn) upon reasonable request and with appropriate approvals, at any time after publication.

Ethics Approval and Informed Consent

This clinical trial was approved by the medical science research ethics committee of Peking University Third Hospital (Approval No: 2024-039-01) and conducted according to the International Conference on harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. This study was registered with ClinicalTrials.gov (NCT06344533). Written informed consent was obtained from each subject before initiation of any study procedures.

Consent for Publication

All the authors know the content and agreed for publication.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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