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ARTICLE

Pharmacokinetics, pharmacodynamics, and safety of frunexian in healthy Chinese volunteer adults: A randomized dose-escalation phase I study

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Abstract

The purpose of this study was to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of frunexian (formerly known as EP-7041 and HSK36273) injection, a small molecule inhibitor of activated coagulation factor XI (FXIa), in healthy Chinese adult volunteers. This study was a randomized, placebo- and positive-controlled, sequential, ascending-dose (0.3/0.6/1.0/1.5/2.25 mg/kg/h) study of 5-day continuous intravenous infusions of frunexian. Frunexian administration exhibited an acceptable safety profile with no bleeding events. Steady state was rapidly reached with a median time ranging from 1.02 to 1.50 h. The mean half-life ranged from 1.15 to 1.43 h. Frunexian plasma concentration at a steady state and area under the concentration–time curve exhibited dose-proportional increases. The dose-escalation study of frunexian demonstrated its progressively enhanced capacities to prolong activated partial thromboplastin time (aPTT) and inhibit FXIa activity. The correlations between PK and PD biomarkers (aPTT/baseline and FXI clotting activity/baseline) were described by the two E_{max} models, with the EC_{50} values of 8940 and 1300 ng/mL, respectively. Frunexian exhibits good safety and PK/PD properties, suggesting it is a promising candidate for anticoagulant drug.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

FXIa is a clinically validated target for the prevention of thrombosis by selectively inhibiting the activation of the intrinsic pathway, without impacting normal hemostasis through the extrinsic pathway.

WHAT QUESTION DID THIS STUDY ADDRESS?

Frunexian, a potent and selective small molecule FXIa inhibitor, demonstrated selective and effective inhibition of the intrinsic coagulation pathway, desirable pharmacokinetics, and safety profile in this Phase I clinical trial.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Frunexian administration in healthy Chinese volunteer adults exhibits favorable safety profiles with no bleeding events, predictable PK, and dose-proportional PD.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Our results position frunexian as a promising candidate for anticoagulant therapy and support its initiation of phase II clinical trials.

INTRODUCTION

Thrombosis is the underlying pathophysiology in the three primary cardiovascular diseases: ischemic heart disease, stroke, and venous thromboembolism.[1] It is estimated that one in every four global fatalities is related to thrombotic conditions, thereby constituting the fourth major contributor to global mortality and years of life lost.[2] Traditional anticoagulants, such as heparin and warfarin, exhibit significant anticoagulation effects but are also associated with severe bleeding complications.[3,4]

Activated factor XI (FXIa) is a serine protease homodimer, essential for maintaining the intrinsic coagulation pathway and playing a pivotal role in amplifying the clotting cascade.[5] FXIa primarily catalyzes the activation of factor IX to factor IXa, subsequently leading to the activation of factor X to factor Xa in the common coagulation pathway.[5] It has been reported that blockade of FXIa by small molecule inhibitor dose-dependently inhibited arterial thrombosis and cerebral microembolic signals in rabbits, suggesting that FXIa inhibition may be a novel therapeutic strategy for reducing microembolic signals in patients with ischemic stroke.[6] Observational studies suggest that individuals with congenital FXI deficiency have a lower incidence of thrombotic events compared to those with normal FXI levels, with no increased risk of spontaneous bleeding.[7,8] Given its intrinsic anticoagulant properties and the lack of impact on physiological coagulation, inhibiting the FXI/XIa pathway may be a promising mechanism for developing novel anticoagulants.

Frunexian is a potent and selective small molecule inhibitor of FXIa. Frunexian can disrupt the essential role of FXIa in the contact-activated thrombin generation process while concurrently suppressing its significant enhancing role in tissue factor-initiated thrombin generation. The results of a previous Australian trial indicate that the maximum dose of frunexian (0.6 mg/kg/h, administered continuously for 5 days) led to a prolongation of activated partial thromboplastin time (aPTT), with a ratio to the baseline of approximately 1.7.[9] At this dose, no serious adverse events or deaths occurred, and the risk of bleeding was low. Therefore, a larger exploratory dose (0.3–2.25 mg/kg/h) was utilized in our study to assess the safety, pharmacokinetic (PK), and pharmacodynamic (PD) characteristics of continuous intravenous infusion of frunexian for 5 days in healthy Chinese adult volunteers.

METHODS

The clinical trial was conducted at the Clinical Pharmacology Center of the Second Affiliated Hospital of Zhejiang University School of Medicine from April 8, 2022 to September 12, 2022 (NCT05742126). The design, implementation, and reporting of this study were conducted in accordance with Good Clinical Practice (GCP), Helsinki Declaration, and relevant regulations of the National Medical Products Administration (NMPA) in China. The protocol, amendments, informed consent forms (ICF), and any updated study documents of this trial were reviewed and approved by the Human Research Ethics Committee of 2nd Affiliated Hospital, School of Medicine, Zhejiang University. All volunteers were required to provide written informed consent prior to screening.

Study design

This study was a randomized, placebo, and positive-controlled study. The study was planned to enroll 54 healthy subjects for a continuous 5-day intravenous infusion (Figure S1). The doses of frunexian were 0.3 mg/kg/h, 0.6 mg/kg/h, 1.0 mg/kg/h, 1.5 mg/kg/h, and 2.25 mg/kg/h, respectively. The dose of heparin sodium was 8 IU/kg/h. The subjects were divided into five dose panels: the first and second dose panels, each consisting of 12 healthy subjects (8 + 2 + 2, frunexian + placebo + heparin sodium), and the other three dose panels, each consisting of 10 healthy subjects (8 + 2, frunexian + placebo). After qualifying through screening, subjects were assigned a randomization number in the order of screening number, and

each randomization number corresponded to a blinded treatment allocation.

Study population

Healthy male and female volunteers between the ages of 18 and 45, with a body mass index (BMI) ranging from 18 to 28 kg/m^2, who were willing to participate in the study and comply with the study requirements, were recruited for the research. During the screening period, subjects were assessed for eligibility based on medical history, physical examination, vital signs, 12-lead electrocardiogram, and laboratory tests to ensure they met the inclusion criteria for the study and had no clinically significant abnormal findings.

Sample collection

In the 0.3 mg/kg/h dose panel, PK (2.0 mL) and PD (5.0 mL) blood samples were collected within 1 h before the study drug injection, and 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 48, 72, 96, 120, 120.25, 120.5, 121, 121.5, 122, 124, 128, 132, and 144 h after frunexian administration.

In the 0.6 mg/kg/h dose panel, PK (3.0 mL) blood samples were collected within 1 h before the study drug injection, and 0.083, 0.25, 0.5, 1, 1.5, 2, 8, 24, 48, 96, 120, 120.25, 120.5, 121, 121.5, 122, 124, 128, 132, 144, 168, and 192 h after frunexian administration. PD (6.0 mL) blood samples were collected within 1 h before the study drug injection and 0.083, 0.25, 0.5, 1, 1.5, 2, 8, 24, 48, 96, 120, 120.25, 120.5, 121, 121.5, 122, 124, 128, 132, and 144 h after frunexian administration.

In the 1.0, 1.5, 2.25 mg/kg/h dose panels, PK (2.0 mL) and PD (6.0 mL) blood samples were collected within 1 h before study drug injection, and 0.083, 0.25, 0.5, 1, 1.5, 2, 8, 24, 48, 96, 120.25, 120.5, 121, 121.5, 122, 124, 128, 132, and 144 h after frunexian administration.

A brief description of the quantification methods of PK and PD blood samples can be found in Appendix S1.

PK and PD parameters

The Phoenix WinNonlin (version 8.3; Certara, Princeton, NJ, USA) was used to estimate PK and PD parameters using a noncompartmental method.

The PK parameters included area under the concentration–time (AUC) curve from time 0 to 24 h (AUC_{0-24h}), AUC from time 0 to 144 h (AUC_{0-144h}), terminal elimination half-life ($t_{1/2}$), clearance (CL), apparent volume of distribution (V_d), time to reach steady state (T_{ss}, first time point with concentration > 90% of average concentration for remainder of Day 1), and concentration at T_{ss} (C_{ss}).

aPTT, prothrombin time (PT), activated clotting time (ACT), and FXI clotting activity (FXI:C) were used as PD biomarkers. The PD parameters included the observed maximum drug effect value after administration (E_{max}), the time to reach the maximum drug effect (T_{Emax}), and the area under the effect-time curve from time 0 to the time of the last quantifiable drug effect value (AUEC).

PK/PD modeling and model evaluation

The relationships between PD biomarkers (the ratios of aPTT/FXI:C to baseline) and plasma concentrations of frunexian were estimated by the Hill equations. The formulas for both models are as follows:

$$\frac{\text{aPPT}}{\text{baseline}} = \text{BSLN} + \frac{C^{\gamma} \times E_{max}}{EC_{50}^{\gamma} + C^{\gamma}}; \frac{\text{FXI: C}}{\text{baseline}} = \text{BSLN} - \frac{C^{\gamma} \times E_{max}}{EC_{50}^{\gamma} + C^{\gamma}}$$

where BSLN, E_{max}, EC_{50}, C, and γ represent baseline, maximum effect, concentration at which the effect achieves half of its maximal change, plasma concentration of frunexian, and the Hill coefficient. BSLN was fixed to 1 in this study. Visual inspection of goodness-of-fit plots, including the relationship between observed value and individual predicted value (IPRED) or population predicted value (PRED), and the relationship between conditional weighted residuals (CWRES) and PRED or time, was performed to assess the models.

NONMEM (version 7.4.0, ICON Development Solutions, Ellicott, Maryland, USA), Perl-speaks-NONMEM (PsN, version 4.8.1, University of Uppsala, Uppsala, Sweden), and the interface software Pirana (version 2.9.4, Certara, Princeton, NJ, USA) were used to perform the PD analysis.

Safety assessments

From the time of signing the ICF until the end of the follow-up period, all adverse events (AEs) occurring were recorded. The safety was assessed based on: 1. a medical review of AEs; 2. clinical laboratory tests; 3. vital signs; 4. physical examinations; 5. ECGs; 6. local reactions at the infusion site. The severity of AEs was recorded according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0). The causal relationship between the drug and AEs was classified into five categories: "definitely related," "probably related," "possibly related," "possibly unrelated," and "definitely unrelated."

Statistical analysis

A comprehensive description of all AEs occurring in subjects within each group was performed, summarizing the cases and incidences of: all AEs, study drug-related AEs, Grade 3 or above AEs, serious AEs (SAEs), AEs leading to discontinuation, and AEs leading to death.

Average drug concentration–time profiles were generated based on plasma drug concentrations detected at each sampling time point. Descriptive statistics for PK parameters were calculated in each dose panel. Dose proportionality was evaluated using a power model. Specifically, a mixed-effects model was employed, with the logarithm of the PK parameters (C_{ss}, AUC_{0-24h}, and AUC_{0-144h}) as dependent variables, the logarithm of dose as a fixed effect, and subject intercept and subject slope as random effects. The point estimate and 90% confidence interval for the slope β were calculated.

Measurement values of aPTT, PT, and ACT, as well as changes and ratios relative to the baselines, were plotted over time according to panels. In addition, the percentage change from baseline was also presented for FXI:C. Summary PD parameters were described as the mean (SD) or median (minimum, maximum) by group.

RESULTS

Participants

A total of 290 healthy subjects were screened for this trial. 58 subjects were successfully enrolled. Out of these 58 enrolled subjects, 4 were excluded prior to medication administration due to abnormal vital signs, electrocardiogram readings, or blood pressure measurements. In addition, 1 and 2 subjects in the 0.6 mg/kg/h and 2.25 mg/kg/h dose panels, respectively, experienced hepatic function abnormalities and drug administration was discontinued. Ultimately, a total of 51 subjects successfully completed the entire clinical study. Study screening, grouping, and completion details are presented in Figure S2. Among all subjects who were randomized and received the investigational drug, the mean (±SD) age was 31.0 (±5.96) years. There were 27 male participants (50.0%) and 27 female participants (50.0%). The Han ethnicity accounted for 52 participants (96.3%). The detailed demographic characteristics are presented in Table 1.

Pharmacokinetics

The plasma concentration–time curves (semi-logarithmic scale) are presented in Figure 1. Steady state was rapidly achieved in all dosage groups after administration, with median T_{ss} ranging from 1.02 to 1.50 h. The summary statistics for C_{ss} and AUC are provided in Table 2. The inter-subject variability of frunexian exposure was low (CV%: 9.7%–19.9% for C_{ss}, 8.3%–20.9% for AUC_{0-24h}, 10.0%–24.6% for AUC_{0-144h}). Results from the mixed effect model (Table S1) indicated that the slope estimates and 90% CIs of C_{ss}, AUC_{0-24h}, and AUC_{0-144h} were 1.05 (95% CI: 0.99–1.12), 1.06 (95% CI: 1.00–1.12), and 1.03 (95% CI: 0.96–1.10). The drug exposure (including C_{ss}, AUC_{0-24h}, and AUC_{0-144h}) was linearly in the dose range of 0.3–2.25 mg/kg/h frunexian administration.

Following the end of infusion, the blood concentration of frunexian rapidly declined, and the mean $t_{1/2}$ was consistent across the dosage groups, ranging from 1.15 to 1.43 h. This indicates that the drug was quickly eliminated from the body after the infusion was stopped. The mean CL ranged from 0.258 to 0.333 L/h/kg, and the mean V_d ranged from 0.521 to 0.677 L/kg (Table 2). These findings suggest that within the dose range of 0.3 mg/kg/h to 2.25 mg/kg/h, there was no observable dose-dependent change in the elimination pattern of frunexian.

Pharmacodynamics

All 54 healthy Chinese adult volunteers who received frunexian, heparin sodium, or placebo were included in the PD analysis. After continuous intravenous infusion of frunexian for 5 days, the aPTT exhibited a clear dose-dependent prolongation. No changes were observed in ACT and PT with variations in dosage (Figure 2). During the administration period, the frunexian group showed a higher ratio of aPTT to baseline compared to the heparin sodium group at various blood collection points. Moreover, this difference increased with the escalating dose of frunexian.

The summary statistics for PD parameters are presented in Table S2. The maximum aPTT ratio to baseline (mean) was 1.33, 1.46, 1.59, 1.80, and 1.92 in frunexian (0.3–2.25 mg/kg/h), 1.04 in placebo group, and 1.12 in heparin sodium groups, respectively. The significant increase in the ratio of aPTT to baseline in the frunexian group compared to placebo showed the effective inhibition of intrinsic coagulation pathway (Figure 3a). Additionally, a significant difference in the ratio of aPTT to baseline was observed in all dosage groups of frunexian and the positive control group.

The inhibition effect of frunexian on FXIa was also dose-dependent. Placebo, 0.3 mg/kg/h, 0.6 mg/kg/h, 1.0 mg/kg/h, 1.5 mg/kg/h, and 2.25 mg/kg/h resulted in average maximum inhibitions of FXIa by −6.07%, −56.14%,

TABLE 1 Demographic characteristics of the subjects.

	0.3 mg/kg/h (*N* = 8)	0.6 mg/kg/h (*N* = 8)	1.0 mg/kg/h (*N* = 8)	1.5 mg/kg/h (*N* = 8)	2.25 mg/kg/h (*N* = 8)	Frunexian (*N* = 40)	Heparin sodium (*N* = 4)	Placebo (*N* = 10)	Total (*N* = 54)
Age, years									
Mean (SD)	31.5 (4.00)	31.4 (7.76)	27.6 (7.29)	31.6 (5.29)	30.3 (5.65)	30.5 (6.03)	34.0 (7.12)	31.9 (5.34)	31.0 (5.96)
Sex, *n* (%)									
Male	4 (50.0)	2 (25.0)	4 (50.0)	5 (62.5)	6 (75.0)	21 (52.5)	2 (50.0)	4 (40.0)	27 (50.0)
Female	4 (50.0)	6 (75.0)	4 (50.0)	3 (37.5)	2 (25.0)	19 (47.5)	2 (50.0)	6 (60.0)	27 (50.0)
Race, *n* (%)									
Han ethnicity	7 (87.5)	8 (100)	8 (100)	8 (100)	8 (100)	39 (97.5)	3 (75.0)	10 (100)	52 (96.3)
Yi ethnic minority	1 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.5)	1 (25.0)	0 (0)	2 (3.7)
Height, cm									
Mean (SD)	164.75 (10.790)	165.76 (7.630)	163.33 (6.940)	163.23 (7.087)	167.14 (7.981)	164.84 (7.919)	163.45 (8.479)	162.14 (8.752)	164.24 (8.023)
Weight, kg									
Mean (SD)	63.15 (11.079)	61.06 (9.613)	58.19 (7.431)	63.13 (8.196)	63.54 (5.585)	61.81 (8.386)	58.18 (11.200)	63.16 (10.387)	61.79 (8.861)
BMI, kg/m^2									
Mean (SD)	23.29 (1.813)	22.18 (1.494)	21.83 (1.669)	23.49 (2.068)	22.96 (1.946)	22.75 (1.833)	21.80 (2.578)	23.95 (1.695)	22.90 (1.912)

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

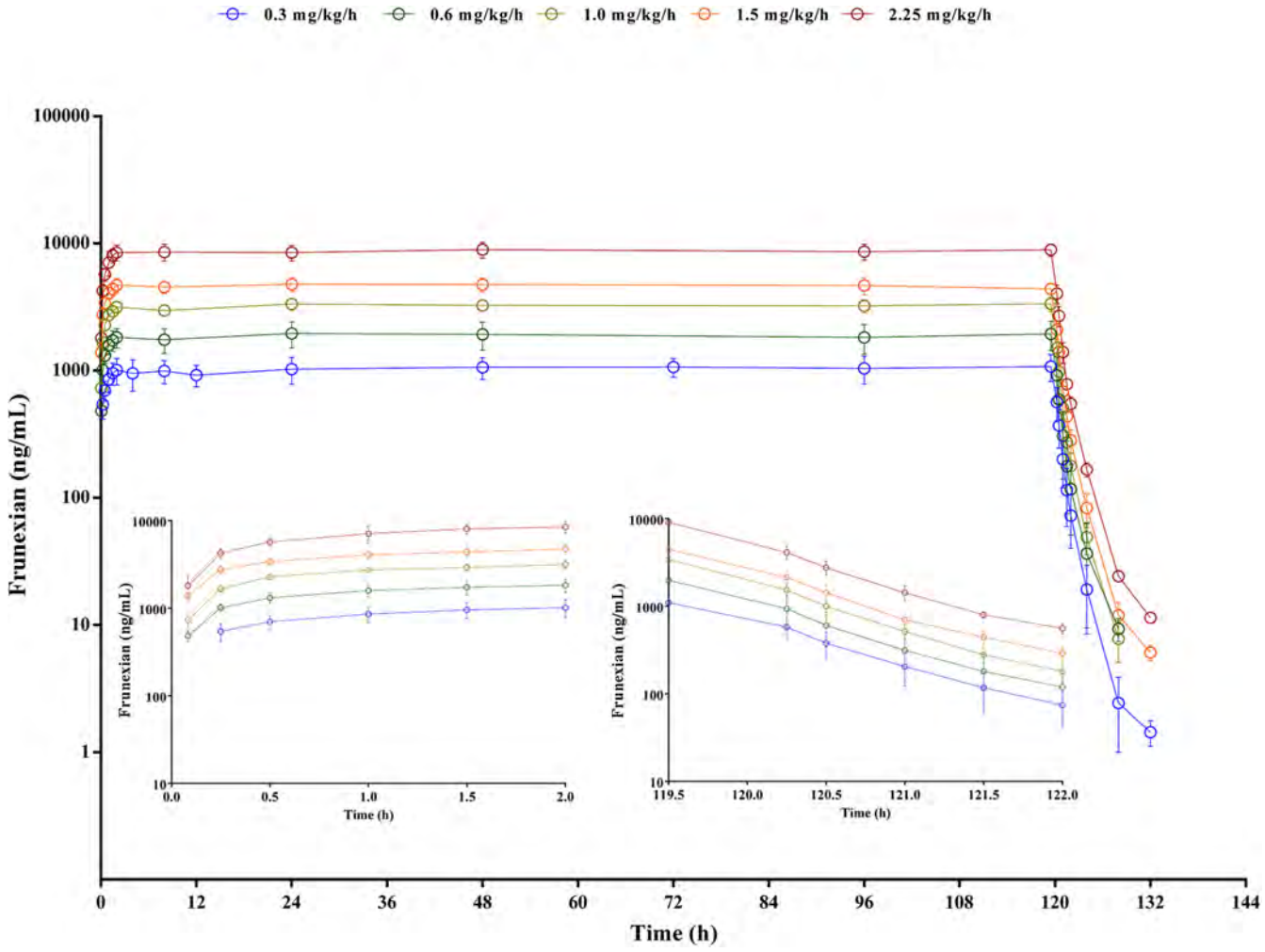

FIGURE 1 Plasma concentration–time profile of frunexian following intravenous infusion over a period of 5 days, including local magnification within 2 h after the initiation and termination of administration. Data are reported as mean ± standard deviation.

−75.21%, −83.25%, −92.25%, and −95.66%, respectively. The analysis of the current individual data revealed a significant inhibition of FXIa in the frunexian group compared to the placebo group (Figure 3b). Notably, no significant difference in FXIa inhibition was observed between the last two dose panels of frunexian, which might suggest saturation of FXIa inhibition by frunexian at high exposures (Figure 3b).

PK/PD correlation

The relationships between plasma concentrations of frunexian and PD biomarkers are presented in Figure 4. The prolongation of aPTT and inhibition of FXIa activity were enhanced with increasing drug concentrations, but both reached a plateau steady-state at higher concentration levels. The estimated parameters of the two PD models are presented in Table 3. The EC_{50} for the ratio of aPTT to baseline was estimated to be 8940 ng/mL, a concentration attained in healthy Chinese volunteer adults following administration of a dosage exceeding 2.25 mg/kg/h. The EC_{50} for the ratio of FXI:C to baseline was estimated to be 1300 ng/mL, a concentration attained in healthy Chinese volunteer adults following administration of a dosage ranging from 0.3 to 0.6 mg/kg/h. The goodness-of-fit plots demonstrated that the final models adequately predicted the observed aPTT and FXI:C values (Figure S3).

Safety and tolerability

A complete listing of AEs by de-identified participants for each study group was presented in Table S3. After excluding expected outcomes attributed to drug efficacy, AEs summarized by group are presented in Table 4. All subjects who received the drug did not experience any serious AEs or bleeding. No Grade 3 or above AEs were reported. Except for one moderate AE of injection site

TABLE 2 The summary statistics of frunexian pharmacokinetics parameters.

	Day 1			Day 1–6	Day 6			
	AUC_{0-24h} (h·ng/mL)	T_{ss} (h)	C_{ss} (ng/mL)	AUC_{0-144h} (h·ng/mL)	λ_z (1/h)	$t_{1/2}$ (h)	CL (L/h/kg)	V_d (L/kg)
0.3 mg/kg/h ($N=8$)	22,512 (20.9%)	1.50 (1.00, 1.52)	937 (19.9%)	122,641 (20.3%)	0.545 (0.0746)	1.30 (0.21)	0.299 (0.0568)	0.546 (0.0545)
0.6 mg/kg/h ($N=8$)	42,555 (20.2%)	1.02 (1.00, 2.00)	1600 (18.0%)	221,431 (24.6%)	0.623 (0.108)	1.15 (0.23)	0.333 (0.0761)	0.544 (0.137)
1.0 mg/kg/h ($N=8$)	73,450 (8.3%)	1.50 (0.98, 2.05)	2994 (10.0%)	387,280 (10.0%)	0.549 (0.0360)	1.27 (0.08)	0.311 (0.0312)	0.568 (0.0598)
1.5 mg/kg/h ($N=8$)	109,172 (10.1%)	1.50 (1.00, 1.50)	4298 (9.7%)	557,843 (11.0%)	0.495 (0.0836)	1.43 (0.23)	0.324 (0.0337)	0.677 (0.158)
2.25 mg/kg/h ($N=8$)	198,246 (14.6%)	1.50 (1.00, 2.00)	7997 (16.1%)	1,052,119 (11.9%)	0.500 (0.0394)	1.39 (0.12)	0.258 (0.0305)	0.521 (0.0886)

Abbreviations: AUC, area under the plasma concentration–time curve; CL, clearance; C_{ss}, concentration at steady state; $t_{1/2}$, terminal half-life; T_{ss}, time to reach steady state; V_d, apparent volume of distribution; C_{ss}, AUC_{0-24h}, and AUC_{0-144h} are described as geometric mean (geometric CV%); T_{ss} is described as median (min, max); λ_z, $t_{1/2}$, CL, and V_d are described as mean (standard deviation).

extravasation in frunexian (1.5 mg/kg/h) and two moderate AEs of hepatic function abnormalities in heparin sodium, all other AEs were categorized as mild in intensity. There was one subject in the 0.6 mg/kg/h dose group, and two subjects in the 2.25 mg/kg/h dose group stopped administration due to abnormal liver function. Three healthy subjects who received the positive control drug in the first two dose groups experienced abnormal liver function. Therefore, the heparin sodium group was removed from subsequent dose panels to ensure subject safety. After excluding AEs related to prolonged aPTT, the incidence rates of study drug-related AEs in the frunexian, heparin sodium, and placebo groups were 10.0%, 100.0%, and 10.0%, respectively. In the frunexian group, all drug-related AEs were abnormal liver function. There was no significant difference in the occurrence of drug-related AEs between the investigational drug and the placebo. Moreover, no correlation was observed between the administered dosage and the occurrence of AEs.

DISCUSSION

Frunexian (formerly HSK36273 and EP-7041) was rapidly absorbed, with exposure being dose-proportional. Parenteral administration of frunexian also showed dose-dependent prolongation of aPTT and suppression of FXIa activity and good safety profiles.

The results of the racial difference analysis indicate that the exposure levels of frunexian in Chinese and Australian subjects under the dose of 0.3 mg/kg/h are similar (90% CI: 80%–125%). At a dose of 0.6 mg/kg/h, Chinese subjects exhibited lower exposure compared to Australian subjects (lower limit of 90% CI slightly below 80%, geometric mean ratio between 0.8 and 0.9). This difference may be attributed to greater individual variability among Chinese subjects; however, overall, exposure levels in China and Australia appear similar. Racial differences may contribute to the observed lower ratios of aPTT peak to baseline in our trial. The results of the relationship between PK and PD showed that FXIa inhibition increased in a non-linear manner. The inhibition of FXIa in the 2.25 mg/kg/h dose panel has reached saturation.

Drugs targeting FXIa can impede the intrinsic coagulation pathway and inhibit the amplification of the clotting cascade, thereby exhibiting antithrombotic effects.[10,11] Clinical trials of FXIa inhibitors have furnished encouraging results in preventing venous thromboembolism.[12] A recent review[13] summarized that 33 trials have been conducted to assess the efficacy/safety of FXIa inhibitors in various indications. FXIa inhibitors developed mainly include ASO (ISIS

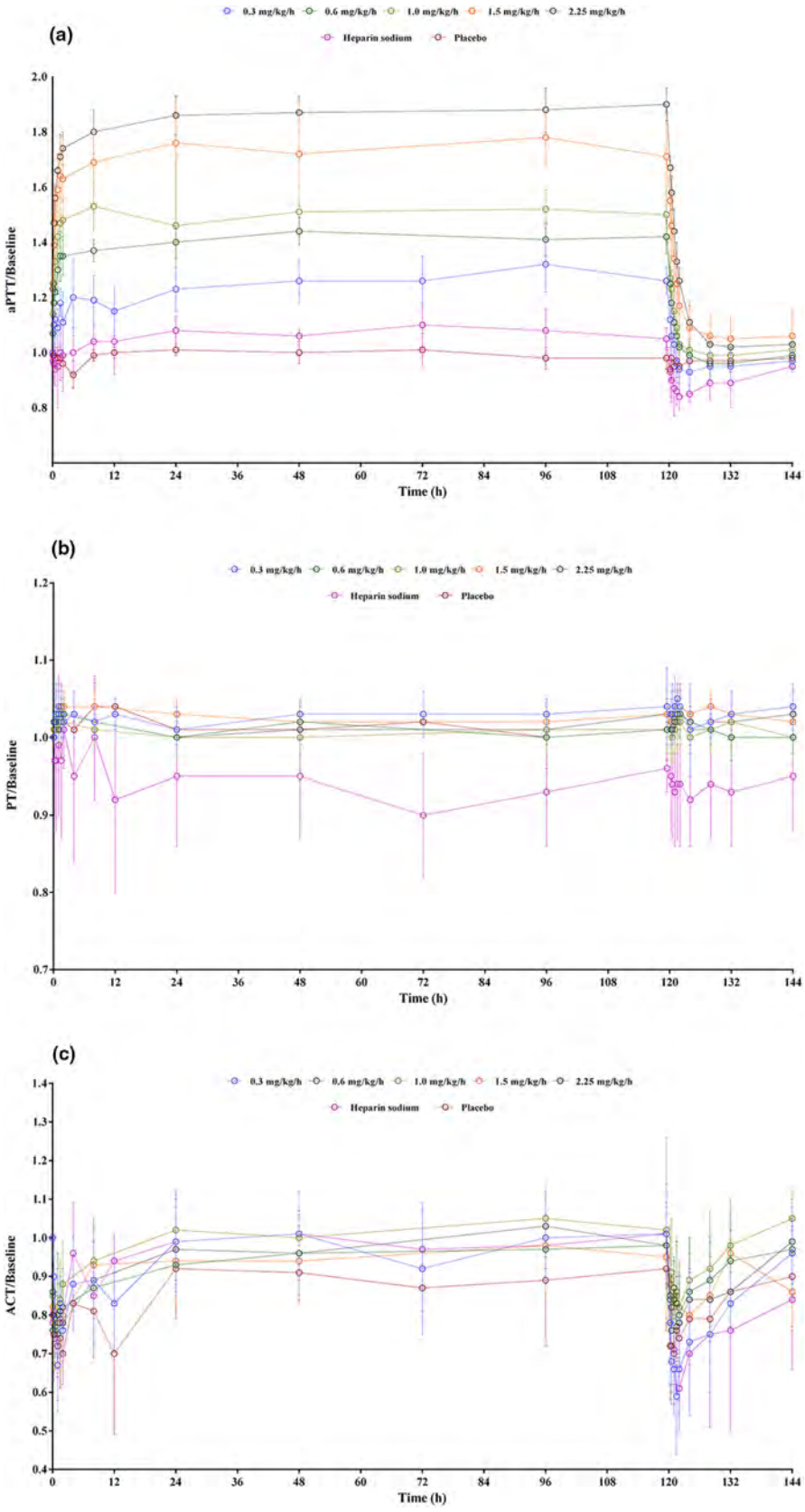

FIGURE 2 Effects of increasing doses of frunexian on aPTT (a), PT (b), and ACT (c) over time in healthy volunteers. Data are expressed as a ratio to baseline and presented as mean and standard deviation.

416858,[14] IONIS-FXIRX[15]), antibodies (MAA868,[16,17] BAY-1213790,[18,19] and AB023[20,21]), and small molecule drugs (frunexian,[22] BMS-962212,[23] BAY-2433334[24]). However, there are currently no drugs on the market.

Two other small molecule FXIa inhibitors administered via intravenous injection, including ONO-7269 (jRCT2080224112), and BMS-962212, have undergone clinical trials. Similar to our study design, a short (2 h)

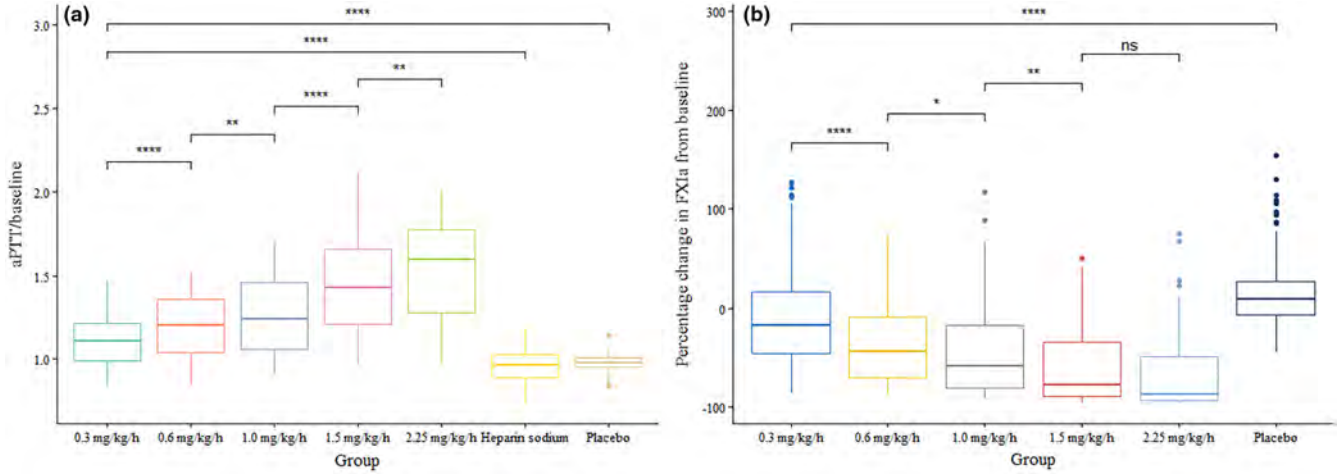

FIGURE 3 Plot of aPTT ratio to baseline (a) and percentage change in FXIa activity from baseline (b) vs. groups. *P*-values were estimated with a two-sided *t*-test analysis. In the box plot, the center lines indicate median values. The lower and upper bounds represent the 25th and 75th percentiles, respectively.

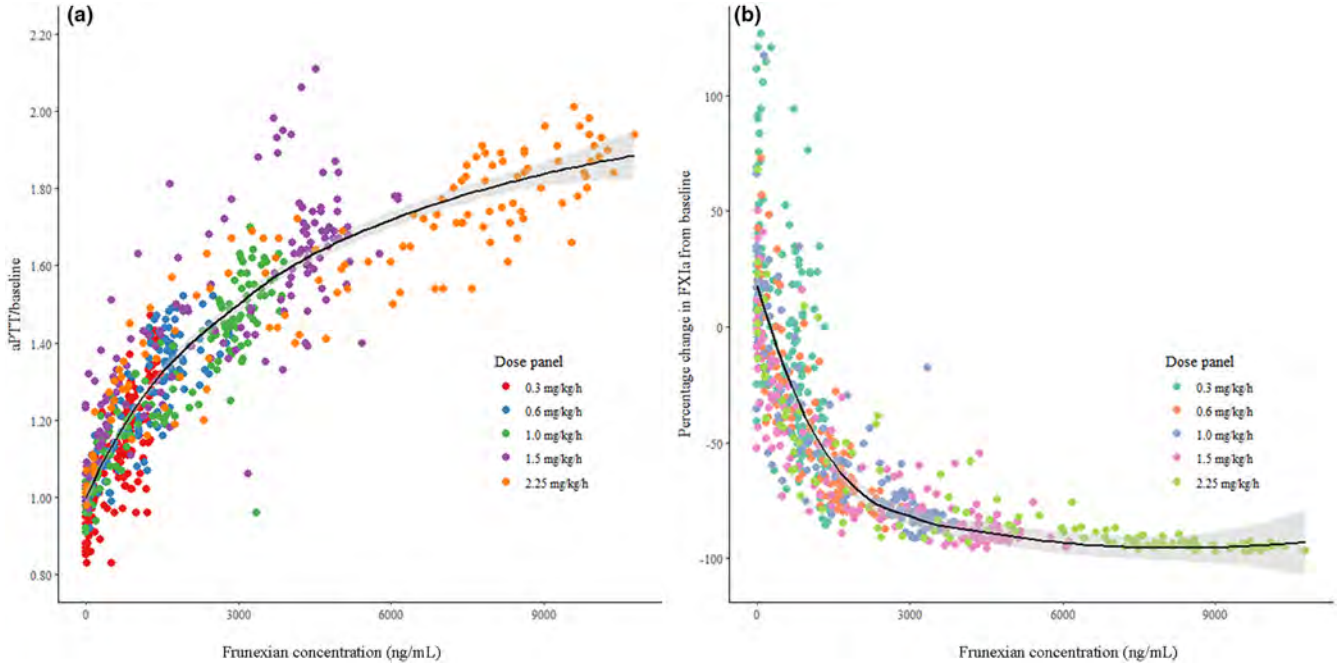

FIGURE 4 Locally weighted scatterplot smoothing (LOESS) regression curves for the relationship between frunexian plasma concentration and aPTT ratio to baseline (a) and percentage change in FXIa activity from baseline (b). Regression curves are represented by solid lines with smoothing based on 95% confidence intervals (shaded areas).

TABLE 3 Estimated parameters of frunexian by the PD models.

	Model for aPTT/baseline		Model for FXI:C/baseline	
Parameters	**Estimates (RSE%)**	**IIV (CV%)**	**Estimates (RSE%)**	**IIV (CV%)**
BSLN	1 (Fix)	0	1 (Fix)	0
E_{max}	1.68 (15%)	8.4	1.03 (2%)	0
EC_{50} (ng/mL)	8940 (37%)	0	1300 (6%)	34.6
γ	0.804 (9%)	23.2	1.4 (9%)	0
$Sigma_{prop}$ (%)	6.1		37.7	
$Sigma_{add}$ (%)	–		–	

Abbreviations: aPTT, Activated partial thromboplastin time; RSE, relative standard error; IIV, inter-individual variability; CV, coefficient of variation; FXI:C, FXI clotting activity.

TABLE 4 Summary of adverse events excluding prolonged aPTT.

	0.3 mg/kg/h (*N* = 8) *n* (%)	0.6 mg/kg/h (*N* = 8) *n* (%)	1.0 mg/kg/h (*N* = 8) *n* (%)	1.5 mg/kg/h (*N* = 8) *n* (%)	2.25 mg/kg/h (*N* = 8) *n* (%)	Frunexian (*N* = 40) *n* (%)	Heparin sodium (*N* = 4) *n* (%)	Placebo (*N* = 10) *n* (%)
Any AE	4 (50.0)	7 (87.5)	3 (37.5)	2 (25.0)	5 (62.5)	21 (52.5)	4 (100)	3 (30.0)
Urine leukocyte esterase-positive	1 (12.5)	4 (50.0)	1 (12.5)	0 (0)	0 (0)	6 (15.0)	1 (25.0)	2 (20.0)
Albuminuria	0 (0)	0 (0)	1 (12.5)	1 (12.5)	4 (50.0)	6 (15.0)	0 (0)	0 (0)
Decreased white blood cell count	2 (25.0)	2 (25.0)	0 (0)	0 (0)	0 (0)	4 (10.0)	4 (100)	0 (0)
Urine occult blood-positive	1 (12.5)	0 (0)	1 (12.5)	1 (12.5)	0 (0)	3 (7.5)	0 (0)	1 (10.0)
Decreased hemoglobin	0 (0)	1 (12.5)	1 (12.5)	0 (0)	0 (0)	2 (5.0)	0 (0)	1 (10.0)
Elevated creatine phosphokinase	1 (12.5)	0 (0)	1 (12.5)	0 (0)	0 (0)	2 (5.0)	1 (25.0)	0 (0)
Elevated neutrophil count	1 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Urine leukocyte-positive	0 (0)	0 (0)	0 (0)	0 (0)	1 (12.5)	1 (2.5)	0 (0)	1 (10.0)
Urine erythrocyte-positive	0 (0)	0 (0)	1 (12.5)	0 (0)	0 (0)	1 (2.5)	0 (0)	1 (10.0)
Urine ketone body-positive	0 (0)	1 (12.5)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Elevated blood uric acid	0 (0)	1 (12.5)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Decreased neutrophil count	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (75.0)	0 (0)
Abnormal liver function	1 (12.5)	1 (12.5)	0 (0)	0 (0)	2 (25.0)	4 (10.0)	3 (75.0)	1 (10.0)
Local injection site erythema and swelling	0 (0)	0 (0)	1 (12.5)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Extravasation at the administration site	0 (0)	0 (0)	0 (0)	1 (12.5)	0 (0)	1 (2.5)	0 (0)	1 (10.0)
Pain at the infusion site	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10.0)
Hypokalemia	0 (0)	0 (0)	1 (12.5)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Diarrhea	0 (0)	1 (12.5)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Mild	4 (50.0)	7 (87.5)	3 (37.5)	1 (12.5)	5 (62.5)	20 (50.0)	2 (50.0)	3 (30.0)
Moderate	0 (0)	0 (0)	0 (0)	1 (12.5)	0 (0)	1 (2.5)	2 (50.0)	0 (0)
Study drug-related AEs	1 (12.5)	1 (12.5)	0 (0)	0 (0)	2 (25.0)	4 (10.0)	4 (100)	1 (10.0)
Abnormal liver function	1 (12.5)	1 (12.5)	0 (0)	0 (0)	2 (25.0)	4 (10.0)	3 (75.0)	1 (10.0)
Decreased neutrophil count	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25.0)	0 (0)
Decreased white blood cell count	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25.0)	0 (0)
Grade 3 or above AEs	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)
AEs leading to discontinuation	0 (0)	1 (12.5)	0 (0)	0 (0)	2 (25.0)	3 (7.5)	0 (0)	0 (0)
Abnormal liver function	0 (0)	1 (12.5)	0 (0)	0 (0)	2 (25.0)	3 (7.5)	0 (0)	0 (0)
AEs leading to death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: aPTT, Activated partial thromboplastin time; AE, adverse event.

and long-term (5 day) intravenous infusion study was performed to assess the safety, PK and PD of BMS-962212.[23] The PK parameters of BMS-962212 exhibited a dose-proportional relationship in both parts. Consistent with our results, BMS-962212 showed exposure-dependent profiles in the prolongation of aPTT and inhibition of FXIa activity. However, BMS-962212, due to longer terminal $t_{1/2}$, may require a longer duration to restore normal physiological coagulation status. The most frequently observed AE for BMS-962212 administration was infusion site pain or irritation (5.9%). Additionally, one healthy subject reported a moderate AE of infusion site erythema. Compared to BMS-962212, frunexian administered in the same manner exhibited relatively better tolerability. Continuous intravenous infusion of frunexian was well tolerated, with rapid onset of action and recovery. Intravenous administration of frunexian could quickly achieve anticoagulation effects and quickly restore normal coagulation.

Our study is limited by some common flaws inherent in a phase I study design. The smaller sample sizes allocated to each group diminish the statistical power when assessing efficacy differences. Additionally, the studies with small sample sizes limit researchers from observing more comprehensive safety outcomes. Second, conclusions drawn from Chinese health volunteers may be challenging to extrapolate to patient populations and other ethnic groups. Lastly, ensuring a constant volume of drug injection by infusion pumps within a unit of time is difficult. The reasons may be related to individual vascular resistance patterns, but this speculation requires further analysis.

CONCLUSION

Frunexian (formerly known as HSK36273 and EP-7041) is expected to be developed as a systemic anticoagulant for clinical application in patients undergoing hemodialysis and surgical procedures. Our findings support further evaluation of frunexian in Phase II/III clinical trials.

AUTHOR CONTRIBUTIONS

J.-y.Z. wrote the manuscript. H.-g.L., Y.-r.W., Y.-m.W., Y.--f.L., and L.-l.W. designed the research. J.-y.Z., Z.-r.R., B.J., D.-d.Y., J.-y.W., Y.H., and H.-g.L. performed the research. J.-y.Z. and Z.-r.R. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

Yong-rui Wang, Yan-mei Wang, Yun-fei Lin, and Ling-ling Wang are full-time employees of Sichuan Haisco Pharmaceutical Co., Ltd. All other authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

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

ETHICAL STATEMENT

The protocol, amendments, informed consent forms, and any updated study documents of this trial were reviewed and approved by the Human Research Ethics Committee of 2nd Affiliated Hospital, School of Medicine, Zhejiang University. The trial was registered on ClinicalTrial.gov (NCT05742126).

CONSENT FOR PUBLICATION

All authors have granted consent for the publication of the manuscript in *Clinical and Translational Science (CTS)*. No personal or clinical details of participants are disclosed.

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SUPPORTING INFORMATION

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

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