

Original Article

Pharmacokinetic and pharmacodynamic properties of ciprofol emulsion in Chinese subjects: a single center, open-label, single-arm dose-escalation phase 1 study

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Abstract: We conducted a single-center, single-arm, open-label, dose-escalation phase 1 clinical trial to evaluate the tolerability of a single intravenous injection of ciprofol emulsion for the induction of short-term general anesthesia. Four doses of ciprofol (0.15 mg/kg, n = 2; 0.4 mg/kg, n = 10; 0.6 mg/kg, n = 6; 0.9 mg/kg, n = 6) were administered. Twenty-four subjects were enrolled, with 18 subjects in the 0.4 to 0.9 mg/kg dosage groups included in the data analysis. In total, 37 mild and 4 moderate adverse events (AEs), including 9 abnormal limb movements (3 moderate cases), 8 cases of sinus bradycardia, 11 cases of prolonged QTcF interval (including 1 moderate case), and 1 case of hypotension, were found, but no serious AEs were reported. The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores rapidly decreased after ciprofol administration. The duration of recovery of the verbal response, loss of verbal response duration, the duration of MOAA/S ≤ 1 and the duration until the return of responsiveness were all increased in a dose-dependent manner. The durations of bispectral index values < 60 (6, 8 and 12 min) were similar to the durations of loss of verbal response (6, 8 and 14 min) and MOAA/S ≤ 1 (5, 5.5 and 13.5 min) in the 0.4, 0.6 and 0.9 mg/kg dose groups, respectively. The plasma concentration reached a peak value approximately 2 min after injection in the 0.4-0.9 mg/kg groups and all subjects fully recovered after ciprofol administration, with the shortest time being 9.2 min in the 0.4 mg/kg group. A ciprofol dosing regimen of 0.4-0.9 mg/kg was well-tolerated and exhibited rapid onset and recovery properties.

Keywords: Anesthetic, ciprofol, pharmacokinetics, pharmacodynamics, sedation

Introduction

Since propofol was first approved for clinical use in 1986, it has become one of the most commonly used intravenous general anesthetic agents, mainly because of its rapid onset and fast recovery characteristics [1-3]. However, a recent trend in pharmacology is to improve the pharmacokinetic (PK), pharmacodynamic (PD) and side effects of similar molecules by modifying the chemical structures of existing drugs [4]. Ciprofol (HSK3486) is a newly developed structural analog of propofol and a short-acting intravenous drug for induction and maintenance anesthesia in adults. Its application includes anesthesia/sedation during invasive

endoscopy and for adult intensive care unit (ICU) patients. The active ingredient of ciprofol is similar to propofol, but with single R-configured diastereoisomers [5]. Besides, in preclinical experiments, the half-maximal effective inhibitory concentration (EC_{50}) of ciprofol on γ -aminobutyric acid type A ($GABA_A$) receptor-mediated currents was 5 times less than that of propofol (5.3 vs. 1.1 μM , respectively) [5]. In addition, the EC_{50} of the loss of the righting reflex in rat, dog and pig was also 5 times less than that of propofol (unpublished data). Phase 1a, 1b clinical trials of ciprofol were completed in Australia and revealed median terminal half-life times ranging from 68.8 to 245.7 minutes for ciprofol doses of 128 to 810 $\mu g/kg$ with

median central nervous system equilibrium half-life time of 1.3 minutes in males and 1.8 minutes in females. Otherwise ciprofol doses of 432 and 540 $\mu\text{g/kg}$ had comparable clinical effects without different adverse event outcomes as 2,500 $\mu\text{g/kg}$ propofol, which is commonly used for anesthesia in clinical practice [6]. Due to potential differences including genetic factors, lifestyle and environment [7-9], we carried out a phase 1 study on Chinese healthy subjects, with the primary endpoint of evaluating anesthetic dose monitoring of ciprofol.

Materials and methods

Conduct of the study

The trial was carried out in healthy adult subjects as a single-center, open-label, single-arm, dose-escalation phase 1 study in the West China Hospital of Sichuan University (Chengdu, China). The ethical committee of our institution approved the trial (approval No. 2016-25). Written informed consent was obtained from all subjects before they were enrolled. The study protocol was registered at ClinicalTrials.gov (registration number: NCT03773835).

Endpoints

The primary endpoint was the evaluation of anesthetic dose monitoring and the secondary endpoint was the evaluation of PD and PK parameters.

Subjects

Briefly, the inclusion criteria for this study were healthy adult male or female subjects, aged 18-49 years, weighing more than 45 kg, with a body mass index (BMI) between 19 and 24 kg/m^2 . Additional inclusion and exclusion criteria are listed in [Supplementary File 1](#).

Procedures

After signing informed consent, subjects who met the inclusion criteria were assigned to the trial in a random sequence and all completed screening tests 21 days prior to commencement of the study. Subjects were initially assigned to 4 ciprofol dose groups (0.15, 0.4, 0.6 and 0.9 mg/kg). The day before the trial started, subjects were accommodated in a standardized phase 1 test room for good clinical practice (GCP).

They were required to fast (no food or liquids of any kind) for at least 8 h before drug administration. PK/PD values were measured and safety items were recorded before and after injection of ciprofol. At the beginning of the trial, 2 subjects in the 0.15 mg/kg group and 4 subjects in the 0.4 mg/kg group were administered medication using infusion pumps. During the administration, it was found that the actual infusion volume of the syringe pump was significantly different from the planned infusion volume, revealing that the infusion volume of the syringe pump was inaccurate. In order to ensure the accuracy of the dosing volume, we decided to change the method of administration to manual injection, which was completed within 1 min. Considering that changing the drug administration method may have had an impact on PK analysis, the subjects who received a drug with the infusion pump were excluded from the PK and PD analysis (**Figure 1**). An anesthetist injected the study drug as a single bolus within 1 min and remained in the test room until a subject's responsiveness returned with normal cardiovascular and respiratory functions. After drug administration, oxygen was administered through an oxygen mask at a flow rate of 10 L/min until the subject was awake. Epinephrine, atropine and metaraminol were prepared but were not administered unless absolutely necessary.

Modified Observer's Assessment of Alertness/Sedation (MOAA/S) [10] scores were assessed once 5 min before drug administration was initiated, which were taken as the baseline value, and then every 1 min for 30 min after administration, and once every 5 min for the next 30 min. If MOAA/S = 5 occurred consecutively 3 times during MOAA/S_{verbal}, stimuli ceased and recovery parameters were carefully recorded. The time to a subject becoming fully alert was determined from the time of the first record for MOAA/S <5 after drug administration until the first measurement of MOAA/S = 5 for 3 consecutive measurements. Heart rate (HR), blood pressure (BP) and a 12-lead real-time electrocardiogram (ECG) were monitored continuously during the trial. After intensive safety, PD and PK assessments in the morning of the second day, subjects left the trial unit and were followed up at 4-7 days intervals (up to 7 days), except for subjects in the 0.6 mg/kg group. Subjects in the 0.6 mg/kg

Pharmacokinetic and pharmacodynamic properties of ciprofol

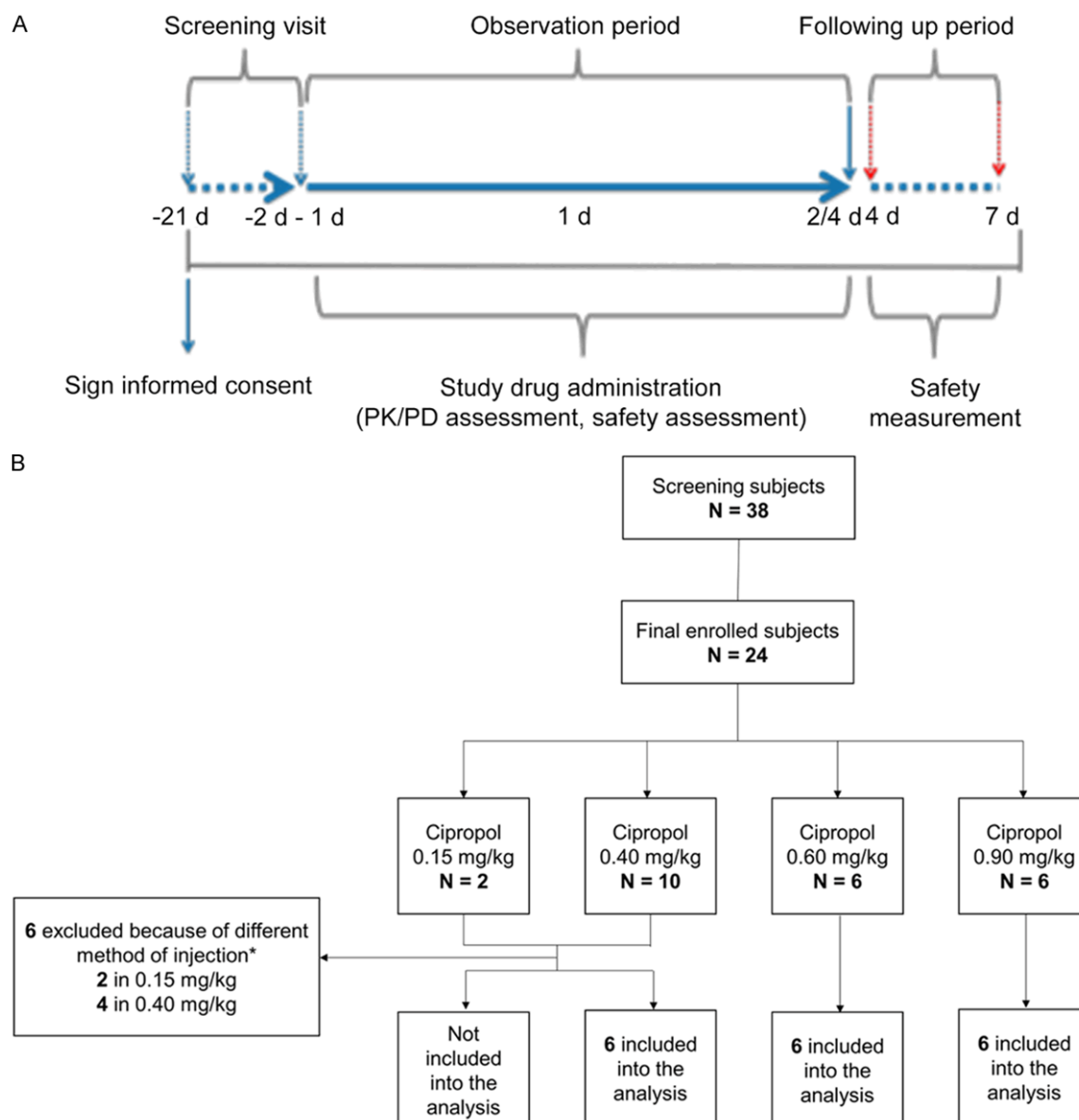


Figure 1. Flow diagrams of the study. A. Scheme of the study periods. B. Scheme of the study subjects. *At the beginning of the experiment, 2 subjects in the 0.15 mg/kg group and 4 subjects in the 0.4 mg/kg group received ciprofol by infusion pump, but the subsequent administrations were changed to manual injections, which were completed within 1 min. Subjects administered medication with an infusion pump were excluded from the PK and PD analyses.

group were required to stay in the hospital to perform 24-48 h urine and 24-72 h fecal tests, and complete the follow-up examination in the morning of day 4. The flow of subjects throughout testing, the study protocol and follow-ups are shown schematically in **Figure 1**.

Safety measurements

Adverse events (AEs) were monitored according to the MedDRA Preferred Term (version

13.0), for the observation period from the administration of the first dose to the last follow-up visit. Investigators monitored vital signs (HR, BP and respiratory parameters), laboratory measurements and a 12-lead ECG during the trial. During drug administration, at least 5 min after completion of anesthesia monitoring placements and establishment of venous access, a 12-lead ECG test was conducted every 5 min for 3 times, and the mean measurement was taken as the baseline value.

Subsequently, data (QT interval, QTcF interval, PR interval, QRS interval, RR interval, ST segment changes and U waves occurrence) were recorded at 0.5 min, 1 min, 2 min, 3 min, 5 min, 8 min, 15 min, 30 min (± 1 min), 1 h (± 2 min), 1.5 h (± 2 min), 2 h (± 2 min), 3 h (± 2 min), 4 h (± 2 min), 6 h (± 3 min), 8 h (± 4 min) and 24 h (± 5 min) after drug administration. If abnormal clinically significant data occurred at any time point, it was carefully recorded. All ECGs were evaluated by a qualified physician for the presence of abnormalities and any clinically significant findings were documented as potential AEs.

When chest wall motion disappeared for longer than 30 s or there was an absence of expired CO_2 waveform for >15 s, it was recorded as apnea and positive airway pressure ventilation was applied. Injection pain was evaluated 0-2 min after trial drug dosing. Mild injection pain was defined as subjects showing small finger movements of the injection hand without obvious withdrawal. Moderate injection pain was defined as subjects showing obvious injection hand movements. Severe injection pain was defined as obvious injection arm withdrawal accompanied by increases in HR and BP. Definitions of AEs and serious adverse events (SAEs) are given in detail in [Supplementary File 2](#) and [Supplementary Table 1](#).

Plasma sampling and PK measurements

All venous blood samples were collected from a venous access in the contralateral arm of the administration site every 30 min before study drug injection and 0.5 min, 1 min, 2 min, 3 min, 5 min, 8 min, 15 min, 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h and 24 h after IV injection. Four mL of blood samples were centrifuged at $2-8^\circ\text{C}$, 3,000 RPM for 10 min to separate out the plasma. These plasma samples were then used to detect PK parameters by Wuxi AppTec (Shanghai, China). Further processing of the plasma samples is described in [Supplementary File 3](#).

Population PK/PD modeling

Clinical PK (plasma concentration), PD (MOAA/S scores and bispectral index (BIS)) data were modeled by Nonlinear Mixed Effects Modelling (NONMEM), and evaluated by bootstrap and graphic methods. Finally, the parameters of the population PK/PD model effect-site elimination rate constant (k_{e0}), the effect-site

equilibration half-time ($t_{1/2k_{\text{e0}}}$) and half-effective target effect-site concentration (C_{e50}) as the main parameters) were obtained. For the population PK model, a one-compartment model, two-compartment model, three-compartment model and a saturable PK model with/without time lag (T_{lag}) were assessed. Since the objective function value (OFV) of the three-compartment model with T_{lag} is the minimum, it was chosen as the basic model of PK. The additive error, proportional error and proportional-additive error models were investigated as statistical models. Among them, the OFV of the proportion-additive error model was the minimum, but the covariance step failed in fitting, so a more stable proportional error model was chosen. In the final models, intra-individual variation was described by the proportional model and inter-individual variation by the exponential model. After evaluation using the bootstrap method and visual predictive checks (VPC), the results indicated that the values of parameters in the original samples were stable and reliable, and that this population PK model could be used to describe the PK characteristics of ciprofol. For the population PK/PD model, the sigmoid E_{max} model with baseline was selected for PD models (BIS and MOAA/S); PK and PD models were linked using an effect-compartment with time lag (T_{elag}). As the OFV in the additive error model was least, the additive error model was selected to describe population PK/PD models. In the final models, intra-individual variation was described by the proportional model and the inter-individual variation was described by the exponential model. Finally, the evaluation results of the bootstrap method and VPC indicated that the values of parameters in the original samples were stable and reliable, and this population PK/PD model could be used to describe the changes of BIS and MOAA/S after administration of ciprofol.

Dose selection

The dose selection (0.15, 0.4, 0.6 and 0.9 mg/kg) for this phase 1 trial was based on the previous published Australian phase 1a and phase 1b clinical trials [6]. Two subjects did not exhibit sedation in the 0.15 mg/kg group (MOAA/S = 5 and BIS value between 96-98). Thus, the study team decided to stop further enrollments for this dose and move to the next highest dose. When escalated to the 0.9 mg/

Table 1. Demographics

	0.4 mg/kg (N = 6)	0.6 mg/kg (N = 6)	0.9 mg/kg (N = 6)
Age*	26.0 (25.0, 27.0)	26.0 (25.0, 27.0)	26.0 (25.0, 27.0)
Height*	168.0 (164.0, 177.0)	160.0 (155.0, 163.0)	164.0 (163.0, 167.0)
Weight*	65.5 (60.1, 74.0)	52.5 (48.0, 58.0)	57.5 (55.5, 65.0)
BMI (kg/m ²)*	23.1 (22.3, 23.6)	21.1 (20.4, 21.8)	21.4 (20.4, 23.6)
Gender, n (%)			
Male	3 (50.0)	3 (50.0)	3 (50.0)
Female	3 (50.0)	3 (50.0)	3 (50.0)

Note: *data are presented as the median (1st to 3rd) quartile.

kg dosage group, all subjects reached deep sedation/anesthesia (loss of verbal response (LOR_{verbal} defined as $MOAA/S < 3$ / $MOAA/S \leq 1$).

After each dose assessment, the study team evaluated all available safety and PD data for ciprofol and collectively agreed on the next escalating dose to be administered.

PD measurements

The depth of sedation/anesthesia was assessed using a MOAA/S score and the BIS value. Loss of eyelash reflexes and orientation recovery were used to assess the onset and offset of sedation/anesthesia. Modified quality of recovery 9 (QoR-9) [11] ([Supplementary Table 2](#)) was used to evaluate the quality of subject recovery from anesthesia after 30 ± 5 min when $MOAA/S \geq 4$, measured before injection and 24 ± 30 min after injection.

Data acquisition and management

The data acquisition and management methods are explained in detail in [Supplementary File 4](#).

Statistical analysis

The sample size was based on other dose-escalation phase 1 studies [12, 13] to ensure adequate subject safety and robust PK/PD data to achieve the objectives of the study. In addition, in order to expose as few subjects as possible to the study medication and procedures, the sample size for each dose group was 6. Data were summarized using descriptive statistics by Statistical Analysis System (SAS, ver. 9.3). Continuous variables were presented as the mean $\pm$ standard deviation (SD) or medians (quartile range). The bootstrap

method was used to evaluate the stability of the population PK/PD models and a total of 1000 bootstrap replications were used to provide the parameter median and confidence intervals (CIs).

Results

A total of 24 subjects were enrolled in the study and 18 were included in the final analysis ([Figure 1](#)). The demographic characteristics were similar among three cohorts ([Table 1](#)).

Safety data

A total of 41 AEs in 18 subjects were reported during the trial. The incidence of AEs was 83.3% (15 of 18 subjects) ([Table 2](#)). Most of the AEs were considered mild in intensity and unrelated to the trial medication. No cases of SAEs were reported in any subject and no subjects withdrew from the trial because of AEs. The AEs considered probably or definitely related to the trial drug were mainly mild abnormal limb movements, sinus bradycardia and prolonged QTcF intervals.

The subjects in the ciprofol 0.4, 0.6 and 0.9 mg/kg groups exhibited a dose-dependent trend in body movements, limb twitches, body twitches, right upper limb twitches, muscle fibrillation and other limb movements within 1-6 min of administration (1 case occurred in the maintenance period, the others in the induction period), with an incidence of 33.3% (2/6), 33.3% (2/6) and 83.3% (5/6). Three AEs, probably related to the trial medication, were moderate, which included 2 cases of abnormal limb movements in the 0.4 mg/kg group and 1 case in the 0.9 mg/kg group. No other dose-related AEs occurred except for abnormal limb movements. There were no

Table 2. The incidence of AEs according to SOC and PT

SOC, PT	0.4 mg/kg (N = 6)		0.6 mg/kg (N = 6)		0.9 mg/kg (N = 6)	
	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events
Total	5 (83.3)	13	5 (83.3)	7	5 (83.3)	21
Nervous system disorders	2 (33.3)	2	2 (33.3)	2	5 (83.3)	5
Abnormal limb movements	2 (33.3)	2	2 (33.3)	2	5 (83.3)	5
Cardiac disorders	4 (66.7)	5	2 (33.3)	2	2 (33.3)	2
Sinus bradycardia	4 (66.7)	4	2 (33.3)	2	2 (33.3)	2
Atrioventricular block	1 (16.7)	1	0 (0)	0	0 (0)	0
Investigations	1 (16.7)	4	1 (16.7)	1	4 (66.7)	7
Prolonged QT interval	1 (16.7)	4	1 (16.7)	1	3 (50.0)	6
Elevated urobilinogen	0 (0)	0	0 (0)	0	1 (16.7)	1
Gastrointestinal disorders	0 (0)	0	1 (16.7)	1	2 (33.3)	2
Thirst	0 (0)	0	0 (0)	0	1 (16.7)	1
Canker sore	0 (0)	0	1 (16.7)	1	1 (16.7)	1
General disorders and administration site conditions	1 (16.7)	1	0 (0)	0	2 (33.3)	2
Medical devices related pain	1 (16.7)	1	0 (0)	0	2 (33.3)	2
Infections and infestations	0 (0)	0	0 (0)	0	1 (16.7)	1
Influenza	0 (0)	0	0 (0)	0	1 (16.7)	1
Musculoskeletal and connective tissue disorders	1 (16.7)	1	0 (0)	0	0 (0)	0
Musculoskeletal discomfort	1 (16.7)	1	0 (0)	0	0 (0)	0
Psychiatric disorders	0 (0)	0	0 (0)	0	1 (16.7)	1
Dysphoria	0 (0)	0	0 (0)	0	1 (16.7)	1
Vascular disorders	0 (0)	0	1 (16.7)	1	0 (0)	0
Hypotension	0 (0)	0	1 (16.7)	1	0 (0)	0
Eye disorders	0 (0)	0	0 (0)	0	1 (16.7)	1
Blurred vision	0 (0)	0	0 (0)	0	1 (16.7)	1

Note: PT, preferred terms; SOC, systematic organ classification.

changes in hemoglobin saturation levels measured by pulse oximeter (desaturation was defined as $\text{SpO}_2 \leq 95\%$), temperature or the respiration rate during the trial. All subjects had stable vital signs over the entire trial period except for 1 case with hypotension who presented with a low BP before the trial (90/57 mmHg) had begun, and 2 cases of sinus bradycardia (50-54 beats/min) after ciprofol injections, respectively (**Figure 2**). One subject in the 0.6 mg/kg group had the lowest BP (89/51 mmHg) before ciprofol administration, with a baseline value of 90/57 mmHg. The systolic BP fluctuated in the range of 82-89 mmHg in the 5-19 min period after ciprofol administration, with a minimum value of 82/50 mmHg. The subject recovered without any other medication being administered, so it was believed that the hypotension was likely related to ciprofol. Another subject in the 0.9 mg/kg group had a baseline HR of 67 beats/min before ciprofol administration, and developed a mild sinus bradycardia (50-54 beats/min, lasting 5 min) 38 min after administration, which

was relieved after brief treatment with atropine, followed by repeated minor fluctuations (around 54 beats/min). No hypotension or other ECG abnormalities were observed during this period and the HR returned to the baseline value at approximately 90 min after ciprofol administration. Due to the normal HR before ciprofol administration and the development of an abnormal rate after administration, it was assumed that the occurrence of this sinus bradycardia was most likely related to ciprofol. A second subject in the 0.9 mg/kg group had a baseline HR of 57 beats/min before ciprofol administration, and developed a mild sinus bradycardia (<60 beats/min, lasting 5 min) 2 min after administration. The treatment regimen and HR fluctuation of this subject was similar to the previous one, but the recovery time of this subject took more than 4 h. Since this subject had a low HR before ciprofol administration and a slight HR fluctuation after administration, it was deemed that the occurrence of this sinus bradycardia was possibly related to ciprofol.

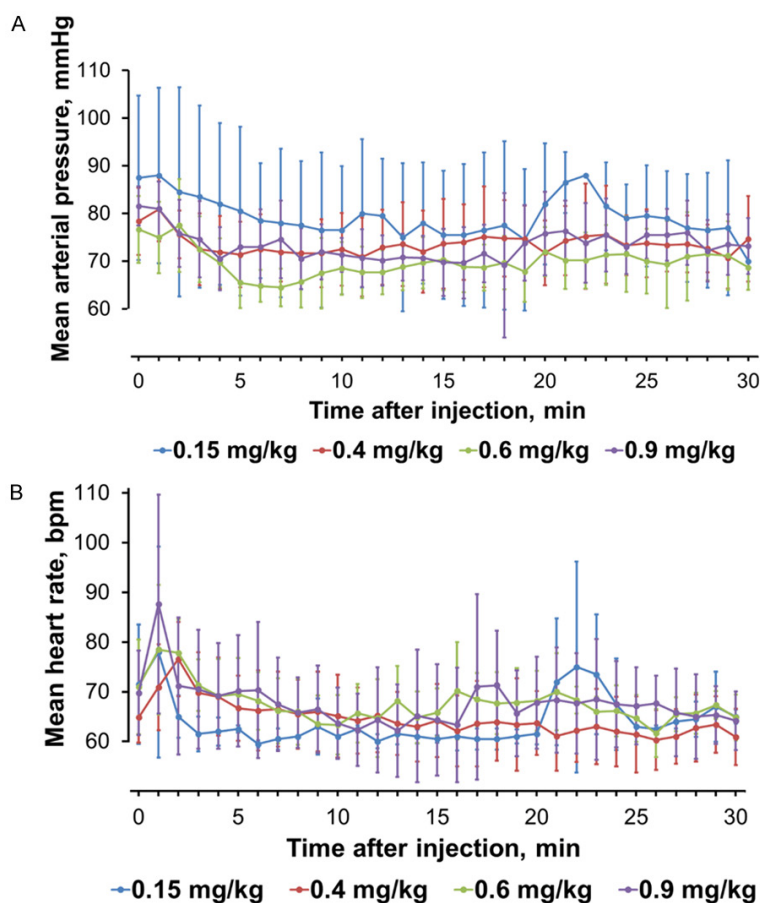


Figure 2. Changes in (A) mean MAP (mmHg), (B) mean HR (beats/min) for each ciprofol group.

Drug-related QTcF intervals were prolonged in 3 subjects (1 in the 0.6 mg/kg group and 2 in the 0.9 mg/kg group). No dose-dependent relationship between the ciprofol doses administered and prolonged QTcF intervals was detected. Injection pain, nausea or vomiting was not experienced by any subject who took part in the study. Laboratory blood and urine tests revealed no abnormalities before and 24 h after injections of ciprofol ([Supplementary Table 3](#)).

PK parameters

The non-compartmental PK parameters are shown in [Table 3](#) and plasma concentration profiles are presented in [Figure 3A](#). Plasma concentrations reached peak levels at 2.0 (2.0, 3.0) min, 2.0 (2.0, 3.0) min, and 2.0 (1.0, 2.0) min in the 0.4, 0.6 and 0.9 mg/kg groups, respectively. Median concentrations at LOR_{verbal} ($C_{p, ROR_{verbal}}$) were 809.5, 768.5 and

1,750.0 ng/mL in the 0.4, 0.6 and 0.9 mg/kg groups, respectively. Recovery of verbal response (ROR_{verbal}) concentrations ($C_{p, ROR_{verbal}}$) were not different among the 3 groups (median: 233.0, 261.0 and 315.0 ng/mL), which suggested that subjects would regain responsiveness when the plasma concentration was about 300 ng/mL ([Table 3](#)). A power function model was used to analyze the proportional relationship between dose and C_{max} , $AUC_{0-\infty}$ and AUC_{0-t} after drug administration. If the 90% confidence intervals (CI) of β fell in the range of 0.80-1.25 (linear interval after dose conversion was 0.725-1.275), it was assumed to be linear. The 90% CIs of the β value for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were 0.257-1.393, 0.257-1.482 and 0.065-1.612, which were all beyond the linear range (0.725-1.275). Due to the small sample size and variations between individual subjects, the present results indicated that ciprofol did not exhibit a linear PK profile in the 0.4-0.9 mg/kg dosage range.

PD parameters

The MOAA/S scores rapidly decreased in all groups after administration of 0.4, 0.6 and 0.9 mg/kg ciprofol. LOR_{verbal} occurred in 83.3%, 100% and 100% of subjects in the 0.4, 0.6 and 0.9 mg/kg groups, respectively. The duration of recover of the verbal response ($T_{ROR_{verbal}}$), LOR_{verbal} duration, the duration of MOAA/S ≤ 1 and the duration until return of responsiveness (duration of first record of MOAA/S < 5 after drug administration to the first record of 3 consecutive times MOAA/S = 5) (T_{alert}) were all increased in a dose-dependent manner ([Figure 3B](#); [Table 4](#)). The durations of BIS values < 60 were 6, 8 and 12 min in the 0.4, 0.6 and 0.9 mg/kg groups, respectively, which were similar to the durations of LOR_{verbal} and MOAA/S ≤ 1 ([Figure 3C](#); [Table 4](#)). In

Table 3. PK parameters and plasma concentration during loss/recovery of the verbal response after ciprofol injection

	0.4 mg/kg (N = 6)	0.6 mg/kg (N = 6)	0.9 mg/kg (N = 6)
$C_{\max}$ (ng/mL)	1,330.0 (985.0, 1,710.0)	1,170.0 (839.0, 1,440.0)	3,060.0 (1,750.0, 3,560.0)
$AUC_{0-30 \text{ min}}$ ($\times 10^4$ min-ng/mL)	0.59 (0.55, 0.71)	0.83 (0.82, 0.85)	1.59 (1.16, 1.78)
$AUC_{0-1 \text{ h}}$ ($\times 10^4$ min ng/mL)	0.82 (0.74, 1.28)	1.19 (1.14, 1.27)	2.07 (1.55, 2.14)
AUC_{0-t} ($\times 10^4$ min-ng/mL)	1.52 (1.36, 2.54)	2.48 (2.26, 2.63)	3.85 (3.25, 4.70)
$AUC_{0-\infty}$ ($\times 10^4$ min-ng/mL)	1.63 (1.47, 3.03)	2.54 (2.44, 2.75)	4.24 (3.37, 5.15)
$T_{\max}$ (min)	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	2.00 (1.00, 2.00)
$T_{1/2z}$ (min)	125.3 (111.8, 148.0)	105.6 (100.1, 125.1)	116.3 (107.9, 602.2)
V_z ($\times 10^3$ mL/kg)	4.3 (2.1, 5.0)	3.6 (3.5, 4.0)	4.3 (4.3, 15.2)
CL (mL/min/kg)	24.6 (13.2, 27.2)	23.7 (21.8, 24.6)	21.7 (17.5, 26.7)
λ_z ($\times 10^{-3}$ L/min)	5.6 (4.7, 6.2)	6.6 (5.5, 6.9)	6.0 (1.2, 6.4)
$MRT_{0-\infty}$ (min)	141.7 (113.1, 142.3)	126.1 (122.0, 132.8)	156.4 (108.6, 404.5)
$AUC_{\% \text{extrap}}$ in %	7.7 (6.7, 12.4)	4.8 (4.4, 7.3)	7.3 (3.5, 9.2)
$C_{p \text{ LORverbal}}^*$	809.5 (149.0, 2,030.0)	768.5 (53.5, 2,960.0)	1,750.0 (386.0, 7,900.0)
$C_{p \text{ RORverbal}}^*$	233.0 (197.0, 242.0)	261.0 (224.0, 362.0)	315.0 (255.0, 361.0)

Note: *Data are presented as the median and range; the remaining data are presented as medians (1st to 3rd) quartiles. $C_{\max}^*$ maximum plasma concentration; AUC , area under the concentration; $T_{\max}^*$, time of maximum plasma concentration; $T_{1/2z}^*$, terminal elimination half-life; CL, clearance; LOR_{verbal}^* , loss of verbal response; ROR_{verbal}^* , recovery of verbal response.

addition, the median (Q1, Q3) time to loss of the eyelash reflex was 105.0 (90.0, 120.0), 90.0 (75.0, 90.0) and 60.0 (60.0, 60.0) s in the 0.4, 0.6 and 0.9 mg/kg groups, respectively. The median (Q1, Q3) orientation recovery time exhibited a dose-dependent increase when ciprofol was administered in doses of 0.4, 0.6 and 0.9 mg/kg [9.0 (7.0, 11.0), 11.0 (9.0, 12.0), and 19.5 (17.0, 21.0) min, respectively]. All modified QoR-9 summary scores were >17 points and recovered to the baseline values after ciprofol administration ceased.

Population PK/PD analyses

Population PK/PD analysis revealed that the population PK model conformed to a time delay three-compartment model ($T_{\text{lag}} = 0.37$ min). The estimated compartmental volumes (V_1 , V_2 and V_3) were 20.5 L, 176.0 L and 61.7 L, and the estimated compartmental clearances (CL_1 , CL_2 and CL_3) were 1.07 L/min, 1.27 L/min and 3.27 L/min, respectively (Table 5). BIS followed a sigmoid $E_{\max}$ model according to baseline values. BIS and the PK model were associated with a time delay at the effect-site concentration (C_e) ($T_{\text{lag}} = 0.455$ min). The estimated median values of model parameters such as C_{e50} , K_{eo} and $t_{1/2K_{eo}}$ were 284.0 ng/mL, 2.2 min^{-1} and 0.315 min, respectively. A

final MOAA/S PD model, established according to the baseline of the sigmoid $E_{\max}$ model and median C_{e50} , was estimated to be 326.0 ng/mL. There was no time delay between C_e connection and the PK model. The estimated median values for K_{eo} and $t_{1/2K_{eo}}$ were 0.626 min^{-1} and 1.11 min, respectively.

Discussion

In Australian phase 1a and 1b trials, subjects tolerated ciprofol at a dosage range of 0.128–0.81 mg/kg, and the proportions of subjects who reached LOR after receiving 0.128 mg/kg, 0.192 mg/kg and ≥ 0.288 mg/kg were 20%, 40% and $\geq 70\%$, respectively [6]. Considering that the initial dosage for this phase 1 trial should be the dosage below the median effective dose (ED₅₀, 50% subjects reached LOR), the median dose of 0.15 mg/kg between 0.128 and 0.192 mg/kg was selected as the initial dose. Taking into account the comparable effect of ciprofol-0.54 mg/kg and propofol-2.0 mg/kg, and the fact that the ciprofol-0.81 mg/kg did not achieve the maximum tolerable dose (MTD) in the previous phase 1a and phase 1b trials [6], doses of ciprofol at 4.0, 6.0 and 9.0 mg/kg were selected for our phase 1 study.

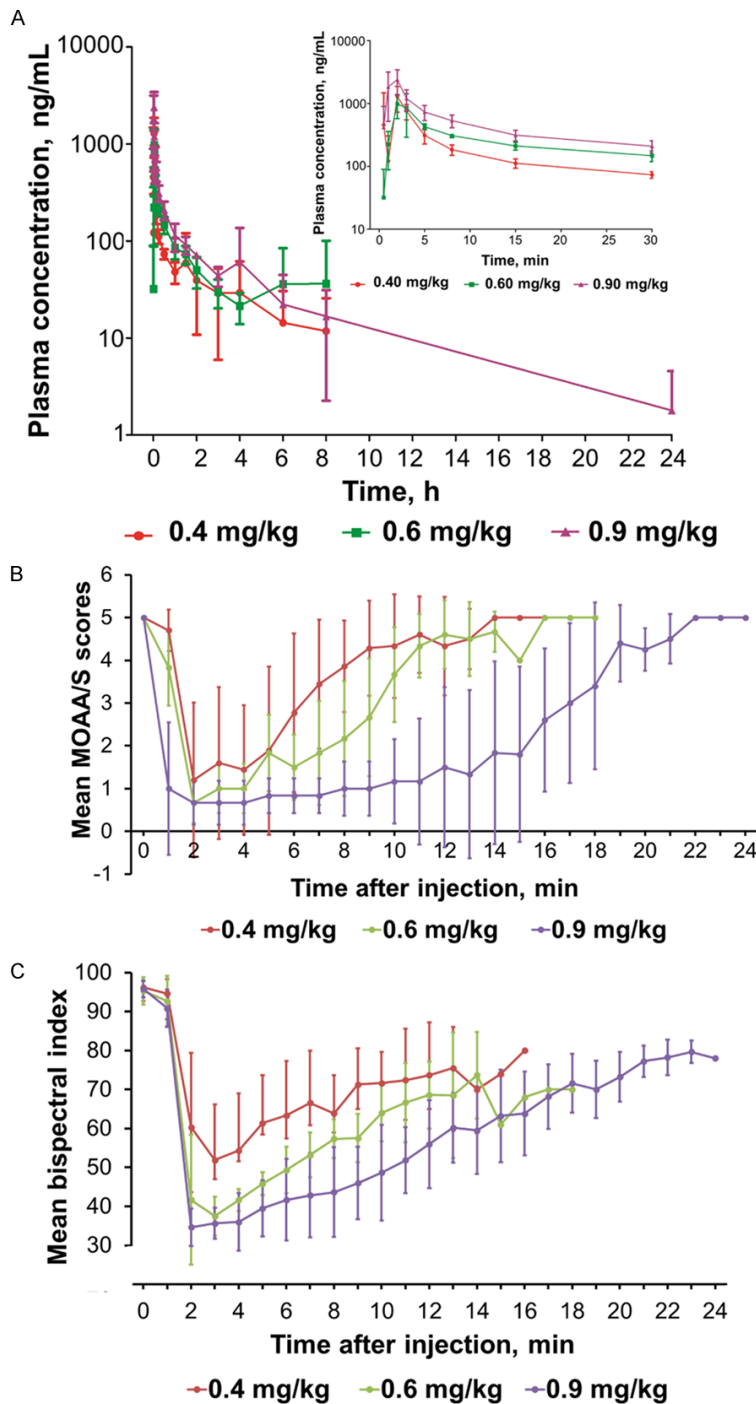


Figure 3. Changes in (A) ciprofol plasma concentrations, (B) MOAA/S scores, and (C) BIS values for each ciprofol group.

Our results showed that ciprofol in a dose range between 0.4 mg/kg and 0.9 mg/kg was well-tolerated. All AEs occurred were mild and only 4 cases of AEs were moderate. The 0.9 mg/kg group of subjects exhibited the highest incidence of abnormal limb movements. The BIS

values of the 3 moderate limb abnormal movement cases were all <60. The frequency of occurrence of abnormal limb movements appeared to increase in a dose-dependent manner, but due to the small sample size, statistical significance was not reached. However, these symptoms may not be indicative of true seizures and other intravenous anesthetics such as etomidate [14] and propofol [15] are known to elicit seizure-like phenomena, similar to those induced by ciprofol in the present study. These abnormal movements may be related to GABAergic inhibition in the central nervous system, which may sensitize the cortex to enter oscillatory excitation states in response to small initial stimuli [16]. Most studies indicate that propofol-induced dystonias and abnormal movements occur in the induction phase [17], which was also the case in the present study after ciprofol administration.

Though QTcF intervals were prolonged in 3 subjects, ciprofol did not induce dose-dependent prolonged QTcF intervals. However, it is noteworthy that QTcF intervals were also prolonged by other general anesthetics including sevoflurane [18, 19], an action attributed to a reduction in the intracellular free Ca^{2+} concentration of cardiac muscle through actions on protein kinase C, thereby inhibiting myocardial contractility [20].

However, for a conclusive assessment on the effects of ciprofol on QTcF intervals, a larger sample size trial will need to be conducted.

BP was slightly decreased (SBP decreased by <10%) for 5 min after injections, but became

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Table 4. MOAA/S and BIS values assessment

	0.4 mg/kg (N = 6)	0.6 mg/kg (N = 6)	0.9 mg/kg (N = 6)
LOR _{verbal} , n (%)	5 (83.3)	6 (100)	6 (100)
ROR _{verbal} , n (%)	5 (100)	6 (100)	6 (100)
T _{LORverbal} (min)	2.0 (2.0, 2.0)	2.0 (2.0, 2.0)	1.0 (1.0, 1.0)
T _{RORverbal} (min)	8.0 (7.0, 8.0)	10.0 (7.0, 10.0)	15.0 (14.0, 17.0)
LOR _{verbal} duration (min)	6.0 (5.0, 6.0)	8.0 (5.0, 8.0)	14.0 (13.0, 16.0)
T _{alert} (min)	7.0 (6.0, 8.0)	9.5 (9.0, 11.0)	19.0 (16.0, 21.0)
MOAA/S ≤1, n (%)	5 (83.3)	6 (100)	6 (100)
MOAA/S ≤1, duration (min)	5.0 (4.0, 5.0)	5.5 (3.0, 7.0)	13.5 (12.0, 15.0)
MOAA/S = 0, n (%)	5 (83.3)	2 (33.3)	4 (66.7)
MOAA/S = 0, duration (min)	2.0 (1.0, 4.0)	2.0 (1.0, 3.0)	6.0 (3.5, 11.5)
BIS _{peak}	41.0 (38.0, 48.0)	34.5 (28.0, 37.0)	29.0 (26.0, 33.0)
T _{BISpeak} (min)	3.0 (3.0, 4.0)	2.5 (2.0, 3.0)	2.5 (2.0, 4.0)
BIS at LOR _{verbal}	56.0 (44.0, 57.0)	38.0 (32.0, 44.0)	89.0 (85.0, 96.0)
BIS at ROR _{verbal}	60.0 (60.0, 63.0)	52.5 (47.0, 57.0)	61.0 (60.0, 64.0)

Note: Data are presented as medians (1st to 3rd quartile) and numbers with percentages. LOR_{verbal}: loss of the verbal response when MOAA/S <3; ROR_{verbal}: recovery of the verbal response when MOAA/S ≥3; T_{LORverbal} (min): duration of loss of the verbal response; T_{RORverbal} (min): duration of recovery of the verbal response; LOR_{verbal} duration (min): duration of LOR_{verbal} and ROR_{verbal}; T_{alert} (min): duration of return of responsiveness (duration of first record of MOAA/S <5 after drug administration to the first record of 3 consecutive MOAA/S = 5); BIS_{peak}: peak BIS value; T_{BISpeak}: the duration when the peak BIS value was reached; BIS at LOR_{verbal}: BIS value at loss of the verbal response; BIS at ROR_{verbal}: BIS value when recovery of the verbal response.

Table 5. Population PK/PD parameters after ciprofol injection

Parameters	Estimated value	1,000 Bootstrapped	
		Median	95% CI
Final PK model			
V1 (L)	20.5	20.6	13.1-26.4
V2 (L)	176	182.7	116.4-290.2
V3 (L)	61.7	60.9	16.4-90.4
CL1 (L/min)	1.1	1.1	0.7-1.3
CL2 (L/min)	1.3	1.3	0.7-2.9
CL3 (L/min)	3.3	3.3	1.9-4.4
T _{lag} (min)	0.4	0.4	0.2-0.5
Final BIS PD model (sigmoid E _{max} model)			
E ₀ , BIS	94.5	94.6	93.5-95.8
E _{max} , BIS	37.1	36.4	31.7-40.9
C _{e50} (ng/mL)	284.0	285.6	253.2-332.8
Keo (min ⁻¹)	2.2	2.3	1.1-5.5
Te _{lag} (min)	0.5	0.5	0.4-0.6
Final MOAA/S PD model (sigmoid E _{max} model)			
E ₀ , MOAA/S	4.7	4.7	4.4-5.0
E _{max} , MOAA/S	0.8	1.0	0.5-1.1
C _{e50} (ng/mL)	326.0	325.0	272.0-365.0
Keo (min ⁻¹)	0.6	0.7	0.5-1.2

stable thereafter (**Figure 2**). In the 0.6 mg/kg group, 1 subject had hypotension (82/50 mmHg), but this may have been due to the subject's initial low baseline value (90/57 mmHg).

In addition, 2 cases of sinus bradycardia occurred, when subjects already had low pulse rates before administration of ciprofol. It should be noted, however, that hypotension and brady-

cardia have been reported as side effects of propofol [21, 22].

In the present trial, we found that ciprofol did not elicit pain in any of the subjects. Injection pain commonly occurs during an IV propofol injection [23]. It has been documented that propofol caused pain or discomfort on injection in 28% to 90% of subjects studied [24-26], while Tan *et al.* reported that several factors can lead to injection pain, including the injection site, vein size, rate of injection, propofol concentration in the aqueous phase and the buffering effect of blood [23].

The PD results showed that the onset and recovery from ciprofol were rapid and produced good quality clinical effects. The MOAA/S scores and BIS results revealed that ciprofol produced sedation in 1-2 min. Loss of the verbal response occurred within 2 min in the 0.4, 0.6 and 0.9 mg/kg groups, which indicated that ciprofol produced a rapid anesthetic effect. $T_{\text{RORverbal}}$, $\text{LOR}_{\text{verbal}}$ duration, a duration of MOAA/S ≤ 1 and T_{alert} all exhibited dose-dependent increases in effects, while the peak BIS values exhibited a decreasing dose-dependent relationship. The duration of BIS values < 60 was also extended with increasing ciprofol dosage.

In addition, the eyelash reflex disappeared within 2 min in the 0.4, 0.6 and 0.9 mg/kg groups. Orientation recovery time increased when the doses of ciprofol ranged from 0.4 to 0.9 mg/kg. The 0.4 and 0.6 mg/kg groups recovered in about 10 min while the 0.9 mg/kg group required about 18 min. All modified QoR-9 summary scores were > 17 points and there was no change in the modified QoR-9 scores compared to the subjects' baseline after recovery from ciprofol. These results indicated that ciprofol had a rapid onset of action and a fast recovery time.

PK parameters for ciprofol were calculated using a non-compartment model. The results revealed that $T_{1/2z}$ for single IV administrations for different doses in healthy subjects was between 2-5 h and the average $T_{1/2z}$ was about 3 h. $T_{1/2z}$ in the 0.4 and 0.6 mg/kg groups was about 2 h and approximately 5 h in the 0.9 mg/kg group. The plasma concentrations of ciprofol at loss of the verbal response ($C_{\text{p, LORverbal}}$) exhibited a large variability in the different dose groups probably due to the rapid distribution of ciprofol into central and peripheral

compartments, while the plasma concentration of ciprofol at recovery of the verbal response ($C_{\text{p, RORverbal}}$) was most likely determined by drug redistribution. Therefore, it is difficult to accurately use $C_{\text{p, LORverbal}}$ determined by drug plasma concentration parameters. These results suggested that subjects regained responsiveness when the plasma concentration fell to about 300 ng/mL.

Limitations of the present study were the small sample size and that the injection mode of the infusion pump was unfortunately difficult to control to inject the drug at a constant volume within 1 min. The reason was probably related to individual vascular resistance patterns, but this conjecture requires further analysis.

In conclusion, a ciprofol dosage regimen of 0.4 to 0.9 mg/kg was well-tolerated and had a rapid onset and fast recovery. A dose of ciprofol > 0.4 mg/kg, which induced deep sedation, is recommended for phase 2 clinical studies. On the basis of these data, further research on the potential usefulness of ciprofol for sedation and/or general anesthesia in endoscopy examinations and sedation of adults in ICUs will be necessary.

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Disclosure of conflict of interest

Xiao Liu and Yong Liang were employees of Sichuan Haisco Pharmaceutical Group Co., Ltd. The remaining authors declared no conflicts of interest.

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Supplementary File 1. Inclusion and exclusion criteria.

The subjects had no potential difficult airway problems nor had previously experienced serious primary diseases of vital organs, including liver, kidney, digestive tract, hemopathy or metabolic disorders.

The exclusion criteria included allergy to either propofol or the ciprofol emulsion components (soybean oil, glycerin, triglycerides, egg yolk lecithin, sodium oleic acid and sodium hydroxide). Subjects who had a history of substance abuse, any symptoms of long-term use of benzodiazepines drugs, or a positive urine drug test were also excluded. Pregnant and lactating females or those who did not want to use medically acceptable forms of birth control during the entire course of the study were also excluded.

Supplementary File 2. AE and SAE definitions.

The Investigator used clinical judgment to determine the relationship between AEs and the investigational drug. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product was considered and investigated. The causal relationship of an AE to the investigated drug was assessed by the investigator (or medically qualified delegate) using the classifications provided in the [Supplementary Table 1](#).

A SAE was any untoward medical occurrence at any dose: 1) resulted in death; 2) was life threatening (i.e. the subject was at immediate risk of death at the time the event occurred; it did not refer to an event which might hypothetically have caused death had it been more severe); 3) required in-subject hospitalization or prolongation of existing hospitalization; 4) resulted in persistent or significant disability/incapacity; 5) was a congenital anomaly/birth defect; 6) was a medically important event or reaction.

Supplementary Table 1. Classification of AEs as associated with drug

Indicator	Definitely related	Probably related	Possible related	Possible not related	Not related
Reasonable time sequence	Yes	Yes	Yes	Yes	Yes
Belongs to the type of reaction known to the study drug	Yes	Yes	Yes	No	No
Reaction may be improved after discontinuation of the study drug	Yes	Yes	Yes or No	Yes or No	Yes or No
Reaction may re-occur with medication	Yes	?	?	?	No
There is another explanation for the reaction	No	No	Yes	Yes	Yes

Supplementary File 3. Plasma sampling and PK measurements.

At first, 100 μ L plasma samples were pretreated for protein precipitation. Then, the plasma concentration of ciprofol was determined using a method of validated liquid chromatography (HPLC; Agilent 1260, Agilent Technologies, Wilmington, DE)-tandem mass spectrometry (LC-MS/MS; API 5500 mass spectrometer, SCIEX, Foster City, CA). The retention time of ciprofol was about 1.6 min, and the calibration curve was calculated by linear regression of the ciprofol peak area (weighting factor $1/x^2$), with a linear range of 5.00 ng/mL to 5,000 ng/mL. All plasma concentration data were acquired and processed by Analyst 1.5.2 (Applied Biosystem, CA, US) and Watson LIMS V7.2.0.02 (PSS, Inc, Wayne, PA) software. The plasma pharmacokinetic parameters, including C_{max} , $AUC_{0-30 \text{ min}}$, $AUC_{0-1 \text{ h}}$, $AUC_{0-\infty}$, T_{max} , V_z , $T_{1/2Z}$, clearance (CL) and mean residence time (MRT) were calculated by a non-compartment model 10. Systemic exposure was estimated as the area under the curve (AUC_{0-t}) from the time of dosing to the last measurable time point (t) by application of the trapezoidal rule using the following equation: $AUC_{(i, i+1)} = (T_{i+1} - T_i) (C_i + C_{i+1})/2$ where AUC_{0-t} is the sum of all $AUC_{(i, i+1)}$. The area under the first moment curve was estimated similarly and extrapolated to infinity according to the following equation: $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$. Of which, C_t was the final determination of plasma concentration. And λ_z was an elimination rate constant, which is the slope of the end segment for the semi-log plasma concentration-time curve calculated using the linear regression method.

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Supplementary Table 2. Modified quality of recovery-9 (QoR-9) questionnaire

QoR-questions	Not at all	Some of time	Most of time
Had a feeling of general well-being	0	1	2
Had support from others (especially doctors and nurses)	0	1	2
Been able to understand instructions and advice. Not being confused	0	1	2
Had a feeling can look after personal toilet and hygiene unaided	0	1	2
Had a feeling can pass urine and having no trouble with bowel function	0	1	2
Been able to breathe easily	0	1	2
Been free from headache, backache or muscle pains	0	1	2
Been free from nausea, dry-retching or vomiting	0	1	2
Been free from experiencing severe pain, or constant moderate pain	0	1	2
Summary score			18

Supplementary File 4. Data acquisition and management.

The Electronic Data Capture (EDC) System was employed in this trial and an electronic case report form (eCRF) was used to collect the data specified in the protocol: the Clinical Study Coordinator (CRC), designated by the principal investigator (PI), timely and accurately input the data from the original medical records into the eCRF, then the data were simultaneously logically-checked by the EDC, and textual data were also manually checked by the data administrator. Once the data from all subjects had been completely and accurately entered, they were reviewed by the PI, sponsor, statisticians and data administrator again to confirm the integrity and accuracy of the database, and finally the database was locked by the data administrator. Subsequently, the data administrator imported appropriate data into the specified database and submitted it to statisticians for statistical analyses.

Supplementary Table 3. Laboratory examinations

	0.40 mg/kg (n = 6)	0.60 mg/kg (n = 6)	0.90 mg/kg (n = 6)
Blood routine			
Hemoglobin (g/L)			
Baseline	147.0 (124.0, 151.0)	142.5 (138.0, 157.0)	145.5 (136.0, 156.0)
24 h of after administration	145.5 (118.0, 151.0)	136.5 (132.0, 155.0)	145.0 (132.0, 158.0)
Red blood cell ($10^{12}/L$)			
Baseline	4.92 (4.25, 5.11)	4.85 (4.60, 5.05)	4.95 (4.59, 5.20)
24 h of after administration	4.87 (3.99, 5.02)	4.70 (4.57, 4.99)	4.85 (4.56, 5.19)
Platelet count ($10^9/L$)			
Baseline	258.5 (249.0, 294.0)	205.5 (170.0, 233.0)	224.5 (204.0, 250.0)
24 h of after administration	235.0 (208.0, 269.0)	208.5 (168.0, 261.0)	207.0 (196.0, 221.0)
White blood cell ($10^9/L$)			
Baseline	5.64 (4.62, 6.94)	5.22 (4.67, 6.23)	5.42 (4.37, 6.26)
24 h of after administration	4.86 (4.31, 7.39)	5.39 (4.95, 6.35)	4.76 (4.46, 6.82)
Neutrophils (%)			
Baseline	58.5 (56.9, 61.7)	57.3 (55.1, 61.0)	57.0 (52.5, 58.9)
24 h of after administration	60.6 (56.2, 65.9)	57.3 (55.3, 60.0)	58.0 (53.4, 64.4)
Lymphocytes (%)			
Baseline	33.0 (32.0, 33.3)	33.9 (27.6, 35.8)	35.0 (31.1, 36.8)
24 h of after administration	30.9 (26.5, 34.4)	33.2 (30.7, 35.8)	32.8 (25.6, 35.9)
Monocytes (%)			
Baseline	5.80 (5.40, 6.00)	7.05 (6.10, 7.40)	6.45 (5.50, 8.10)
24 h of after administration	5.80 (5.20, 5.90)	6.30 (5.40, 6.80)	6.75 (5.70, 8.30)

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Hematocrit (L/L)				
Baseline	0.43 (0.39, 0.44)	0.43 (0.40, 0.45)	0.45 (0.40, 0.46)	
24 h of after administration	0.43 (0.36, 0.44)	0.41 (0.39, 0.45)	0.44 (0.41, 0.47)	
Blood biochemistry				
Aspartate transaminase (IU/L)				
Baseline	19.0 (18.0, 25.0)	19.5 (19.0, 22.0)	20.0 (19.0, 26.0)	
24 h of after administration	18.0 (16.0, 19.0)	17.5 (17.0, 19.0)	19.0 (18.0, 23.0)	
Alanine transaminase (IU/L)				
Baseline	17.5 (11.0, 21.0)	12.0 (11.0, 19.0)	16.5 (13.0, 24.0)	
24 h of after administration	16.0 (9.0, 22.0)	11.5 (8.0, 16.0)	14.5 (10.0, 23.0)	
Alkaline phosphatase (IU/L)				
Baseline	59.0 (52.0, 69.0)	58.5 (53.0, 74.0)	62.0 (60.0, 70.0)	
24 h of after administration	56.5 (52.0, 64.0)	54.5 (49.0, 61.0)	55.0 (54.0, 73.0)	
Lactate dehydrogenase (IU/L)				
Baseline	182.5 (159.0, 196.0)	157.0 (147.0, 160.0)	173.0 (164.0, 192.0)	
24 h of after administration	163.5 (137.0, 174.0)	148.0 (131.0, 168.0)	167.5 (160.0, 171.0)	
Total protein (g/L)				
Baseline	74.5 (72.6, 75.8)	76.1 (72.9, 79.0)	77.7 (74.1, 79.2)	
24 h of after administration	72.6 (67.3, 74.1)	71.5 (70.3, 74.4)	75.5 (73.4, 77.8)	
Albumin (g/L)				
Baseline	48.3 (46.7, 49.5)	50.6 (48.9, 52.9)	49.0 (47.5, 49.6)	
24 h of after administration	45.7 (44.4, 46.8)	47.5 (45.0, 49.9)	47.2 (45.3, 48.6)	
Total bilirubin (μmol/L)				
Baseline	12.3 (11.3, 16.5)	14.9 (12.5, 18.0)	10.8 (9.9, 12.7)	
24 h of after administration	10.6 (9.8, 13.6)	14.0 (10.2, 20.5)	13.4 (9.8, 14.5)	
Ureophil (mmol/L)				
Baseline	3.81 (3.50, 5.50)	5.00 (3.80, 6.19)	4.10 (3.36, 4.60)	
24 h of after administration	4.00 (3.60, 4.40)	3.85 (3.50, 4.30)	3.68 (3.30, 5.10)	
Creatinine (μmol/L)				
Baseline	76.0 (52.0, 90.0)	64.5 (53.0, 73.0)	63.5 (56.0, 66.0)	
24 h of after administration	59.5 (37.0, 77.0)	65.0 (49.0, 81.0)	70.0 (54.0, 72.0)	
Uric acid (μmol/L)				
Baseline	424.0 (276.0, 476.0)	366.0 (230.0, 403.0)	310.0 (268.0, 387.0)	
24 h of after administration	393.0 (235.0, 482.0)	321.5 (247.0, 349.0)	303.5 (253.0, 329.0)	
K (mmol/L)				
Baseline	4.14 (3.97, 4.28)	4.08 (4.00, 4.28)	4.07 (3.89, 4.23)	
24 h of after administration	4.08 (3.97, 4.22)	4.31 (4.07, 4.34)	4.13 (3.78, 4.43)	
Na (mmol/L)				
Baseline	139.9 (138.2, 140.4)	141.2 (139.2, 141.5)	139.1 (138.6, 142.2)	
24 h of after administration	138.2 (137.5, 139.0)	138.9 (138.0, 141.3)	139.0 (135.2, 139.0)	
Ca (mmol/L)				
Baseline	2.28 (2.24, 2.28)	2.39 (2.23, 2.46)	2.37 (2.33, 2.39)	
24 h of after administration	2.21 (2.20, 2.35)	2.33 (2.29, 2.36)	2.30 (2.26, 2.39)	
Mg (mmol/L)				
Baseline	0.81 (0.79, 0.89)	0.84 (0.77, 0.89)	0.82 (0.81, 0.84)	
24 h of after administration	0.81 (0.78, 0.84)	0.79 (0.75, 0.82)	0.78 (0.73, 0.83)	
Triglyceride (mmol/L)				
Baseline	0.86 (0.59, 1.55)	0.81 (0.53, 1.39)	0.83 (0.56, 1.08)	
24 h of after administration	1.08 (0.74, 1.33)	0.94 (0.69, 1.10)	0.96 (0.66, 1.00)	

Pharmacokinetic and pharmacodynamic properties of ciprofol

Cholesterol (mmol/L)				
Baseline	4.41 (4.37, 4.54)	4.43 (4.24, 4.47)	4.38 (3.62, 4.81)	
24 h of after administration	4.20 (4.08, 4.30)	4.23 (4.05, 4.29)	4.09 (3.53, 5.08)	
Low density lipoprotein cholesterol (mmol/L)				
Baseline	2.59 (2.43, 2.99)	2.38 (2.30, 2.44)	2.26 (1.65, 2.69)	
24 h of after administration	2.47 (2.39, 2.72)	2.28 (2.13, 2.31)	2.28 (1.73, 2.81)	
High density lipoprotein cholesterol (mmol/L)				
Baseline	1.28 (1.22, 1.47)	1.59 (1.32, 1.74)	1.62 (1.16, 2.02)	
24 h of after administration	1.21 (1.16, 1.28)	1.43 (1.38, 1.54)	1.48 (1.17, 1.88)	
Glucose (mmol/L)				
Baseline	4.56 (4.35, 4.95)	4.52 (4.20, 4.90)	4.62 (4.39, 5.04)	
24 h of after administration	4.60 (4.49, 4.79)	4.88 (4.58, 5.07)	4.98 (4.76, 5.03)	
Urine routine				
Red blood cell (/uL)				
Baseline	5.00 (3.00, 9.00)	3.50 (1.00, 5.00)	4.00 (1.00, 14.00)	
24 h of after administration	3.50 (2.00, 5.00)	2.50 (1.00, 5.00)	2.50 (1.00, 8.00)	
White blood cell (/uL)				
Baseline	3.00 (1.00, 9.00)	4.00 (1.00, 10.00)	1.00 (0.00, 2.00)	
24 h of after administration	4.50 (1.00, 7.00)	2.00 (1.00, 5.00)	1.50 (1.00, 2.00)	
Troponin (ng/L)				
Baseline	4.75 (3.60, 5.90)	4.85 (3.70, 5.20)	3.55 (3.20, 3.90)	
24 h of after administration	4.90 (4.00, 6.00)	4.35 (3.40, 5.40)	3.75 (3.40, 4.10)	

Note: All data are presented as median (1st to 3rd) quartile.