

Effects of Cipepofol on Cardiac Depolarization and Repolarization in Healthy Subjects: A Single-Center, Randomized, Placebo and Positive-Controlled Thorough QT Study

Robert Kleiman¹, Todd Rudo¹, William Daley², Mengyue Hu³, Pangke Yan³, Rong Zhou³, Jie Hou⁴

¹Cardia Safety, Clario, Philadelphia, PA, USA; ²Haisco-USA Pharmaceutical Company, Inc, Bridgewater, NJ, USA; ³Haisco Pharmaceutical Group Co. Ltd, Chengdu, People's Republic of China; ⁴Phase I Center, Beijing Gobroad Boren Hospital, Beijing, People's Republic of China

Correspondence: Jie Hou, Phase I Center, Beijing Gobroad Boren Hospital, No. 6 South Zhengwangfen, South Third Ring Road, Fengtai District, Beijing, 102200, People's Republic of China, Tel +8618611422958, Email jie.hou@gohealtharo.com

Background: Cipepofol (HSK3486), a gamma-aminobutyric acid type A (GABAA) receptor agonist, has garnered considerable attention as a potential alternative to propofol. This study aimed to evaluate the effects of a single intravenous (IV) bolus dose of cipepofol (0.4 mg/kg) on QTc interval in healthy subjects.

Patients and Methods: This was a single-center, randomized, blinded (except for moxifloxacin), placebo- and positive-controlled study with a six-sequence, three-period crossover study. Subjects were randomized to 1 of 3 treatment groups in each period: Group A (placebo); Group B (single dose of 0.4 g moxifloxacin, positive control); and Group C (cipepofol [HSK3486], 0.4 mg/kg via IV bolus). The primary endpoint was the change-from-baseline in QTc interval, corrected for heart rate (HR) using the individual QT correction method (QTcI) – Δ QTcI. Secondary endpoints included change-from-baseline in other electrocardiographic (ECG) parameters. Safety/tolerability and pharmacokinetics of cipepofol were also assessed.

Results: Forty-eight subjects were randomized, and demographic characteristics were comparable across the six sequences. The LS mean placebo-corrected Δ QTcI ($\Delta\Delta$ QTcI) interval following cipepofol bolus ranged from -1.7 to 4.1 milliseconds. The upper bound of the two-sided 90% confidence interval for $\Delta\Delta$ QTcI interval remained < 10 milliseconds at all post-dose timepoints. In addition, no clinically significant effects of cipepofol were observed on the PR interval or QRS interval (ventricular depolarization time). Assay sensitivity was successfully demonstrated by the expected QTc interval prolongation within 2–4 h post-moxifloxacin administration. No subjects in the cipepofol treatment period developed a new QTcI interval >480 or an increase in QTcI interval from baseline >60 milliseconds. All adverse events were mild to moderate in severity, and no serious adverse events or deaths occurred.

Conclusion: Cipepofol exhibited no clinically relevant effects on the QTc interval or other ECG parameters, and was safe and well tolerated in healthy subjects.

Clinical Trial Registration: This study was registered on ClinicalTrials.gov (NCT06379867).

Keywords: cipepofol, cardiac repolarization, effect, QT/QTc interval, pharmacokinetics, safety

Introduction

Propofol is a widely preferred agent for anesthesia induction; however, it can induce dose-dependent cardiopulmonary depression, leading to adverse events (AEs) such as hypotension, bradycardia, and apnea.¹ This safety concern underscores the need for safer alternatives. Cipepofol (also known as HSK3486 or ciprofol) has emerged as a promising candidate. As a gamma-aminobutyric acid type A (GABAA) receptor agonist structurally related to propofol, cipepofol demonstrates a clinically superior profile, notably by significantly reducing injection pain and the overall incidence of AEs.² These benefits are largely attributable to its distinct chemical structure, 2-(1-cyclopropylethyl)-6-isopropylphenol, which enables a markedly

enhanced binding affinity for the GABAA receptor (approximately 4–5 fold that of propofol) and results in a wider therapeutic safety window.

Approved in China in December 2020, cipepofol has had its clinical value further validated by extensive global trials.³ Over 30 clinical trials have been completed across China, Australia, the United States, and the European Union. These studies encompass a diverse range of participants, including healthy volunteers, intensive care unit patients, and individuals undergoing procedures such as fiberoptic bronchoscopy, colonoscopy, gastroscopy, endoscopy, or elective surgery.^{2–7} A phase I study demonstrated that cipepofol administered at 0.4 mg/kg exhibited striking similarities to propofol (2 mg/kg) in terms of pharmacokinetic, pharmacodynamic, and safety profiles.⁸ Additionally, a systematic review and meta-analysis encompassing 15 randomized controlled trials (2441 patients) confirmed the comparable efficacy between cipepofol and propofol. Notably, cipepofol was associated with prolonged time to full alertness, reduced injection pain, and potentially lower incidences of hypotension and respiratory depression compared with propofol.²

A critical consideration in the further development of the drug is to determine whether it poses cardiac safety concerns.⁹ The evaluation determines whether drug-induced QT interval prolongation occurs, as this biomarker for delayed cardiac repolarization is associated with an increased risk of cardiac AEs. The QT interval, which measures the total duration of ventricular depolarization and repolarization, is inversely related to heart rate (HR). To account for this variability, the QT interval is corrected to yield the corrected QT (QTc) interval, an estimate normalized to a standard HR of 60 beats per minute (bpm).¹⁰ Studies have indicated that QTc values > 500 milliseconds are associated with an increased risk of cardiac events.¹¹ Although the effects of propofol on the QT interval remain a subject of debate, evidence has shown that propofol may induce torsades de pointes (TdP), which is a polymorphic ventricular tachycardia associated with QT prolongation.¹²

A pooled retrospective cardiodynamic evaluation of 5 studies (NCT03773835, NCT04294056, NCT03698617, NCT04037657, NCT04029766) has been conducted to evaluate the effects of cipepofol on QTc interval and other electrocardiographic (ECG) parameters. However, the effects of cipepofol on the QTc interval were found to be inconclusive, with inconsistent evidence regarding QTc interval prolongation immediately following bolus administration. Given the concurrent changes in HR and autonomic tone observed after cipepofol administration, it is challenging to discern whether the QTc interval changes occurring simultaneously with large and rapid increases in HR are directly attributable to the drug or are instead a consequence of these confounding factors.

In May 2005, the International Council for Harmonization (ICH) released the E14 Guidance for Industry, titled “A New Regulatory Guidance on the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential”.^{9,13} This guidance introduced the concept of a thorough QT/QTc study, a dedicated study designed to identify the effects of a new drug on QTc interval and risk of ventricular proarrhythmia.¹⁴ Consequently, a thorough QT (TQT) study was deemed necessary to rigorously evaluate the effects of cipepofol on the QTc interval in healthy volunteers, thereby generating robust cardiac safety evidence to support the global development of cipepofol. The present TQT study was performed to evaluate the effects of a single intravenous (IV) bolus of 0.4 mg/kg cipepofol on cardiac repolarization in healthy subjects. In addition, this study assessed the effects of a single IV bolus of cipepofol (as well as placebo and moxifloxacin as a positive control) on other ECG parameters, the safety and tolerability, and the pharmacokinetics (PK) of cipepofol.

Materials and Methods

Study Design

In accordance with the ICH E14 guideline,¹³ this single-center, randomized, blinded (except for moxifloxacin), placebo- and positive-controlled study with a six-sequence, three-period crossover design was performed in healthy subjects at Beijing Gobroad Boren Hospital from April 9, 2024 to May 19, 2024. Ethical approval was obtained from the Ethics Committee Institutional Review Board of Beijing Gobroad Boren Hospital (approval number: YW2024-003). The study was completed in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP) by the National Medical Products Administration (NMPA) and relevant laws and regulations. All participants signed the informed consent form prior to study enrollment. This study was registered on ClinicalTrials.gov (NCT06379867).

Subjects

Eligible subjects were healthy individuals aged 18 to 45 years, with a body mass index (BMI) of 19–28 kg/m² (male body weight ≥ 50 kg, female body weight ≥ 45 kg), left ventricular ejection fraction $\geq 50\%$, and the ability to understand and comply with protocol requirements were eligible. The main exclusion criteria included: 1) history of clinically significant systemic disease; 2) history of allergy to egg or egg products, soybeans or soy products; 3) history of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substances; 4) clinically significant infection, injury, disease within 1 month prior to dosing; 5) history of hepatobiliary disease, etc. The detailed exclusion criteria are present in [Supplementary Box S1](#). Subjects were discontinued from the study as follows. Withdrawal was done by the subject, ie they refuse to continue to participate, so he/she withdrew their consent or physician caring for the subject. Discontinuation was done by the study sponsor, study site or operation.

Study Drug and Administration

The study employed cipepofol (HSK3486) as the investigational drug, placebo as the negative control, and moxifloxacin as the positive control to assess assay sensitivity.^{14,15} All treatment regimens were provided by Xizang Haisco Pharmaceutical Co., Ltd (China). Healthy subjects were equally randomized to one of six dosing sequences (C-B-A, A-B-C, B-C-A, C-A-B, A-C-B and B-A-C) as shown in [Figure 1](#). The study consisted of three periods, with a 5-day washout period between consecutive periods. Using the Williams design, subjects were randomized into 1 of 3 treatment groups in each period: Group A received the negative control (placebo), Group B received the positive control (a single dose of 0.4 g moxifloxacin hydrochloride tablet), and Group C received the active treatment (cipepofol, a single IV bolus 0.4 mg/kg). Given safety considerations, a supratherapeutic dose of cipepofol was not investigated. The study drug was administered on Day 1 (Period 1), Day 6 (Period 2), and Day 11 (Period 3). All participants were confined to the clinical research unit and closely monitored throughout the 12-day observation period.

Randomization and Blinding

Randomization was performed by an independent, unblinded statistician using SAS version 9.4. Eligible subjects were randomly assigned to treatment groups in sequential order of screening. This statistician also prepared a drug code list that corresponded one-to-one to the subject randomization numbers and supervised the labeling of the study drug kits. The study was double-blinded for

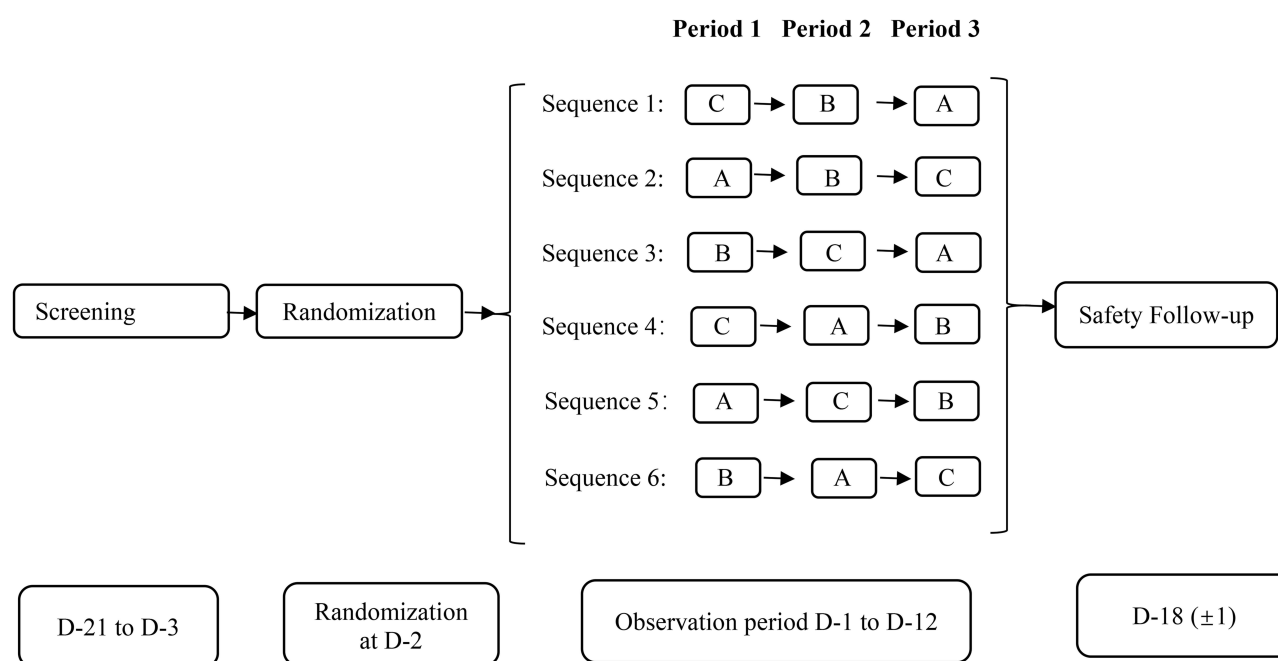


Figure 1 Dosing sequences and visit diagram. (A) Placebo; (B) moxifloxacin; (C) cipepofol.

cipepofol and placebo. To maintain blinding, an identically appearing emulsion for injection was prepared for both cipepofol and placebo. Moxifloxacin hydrochloride tablets were administered using an open-label design. Consequently, the subjects, investigators, and all study site personnel remained blinded to the assignment of the injectable study drugs (cipepofol or placebo).

Assessments and Endpoints

The primary endpoint was the placebo-corrected change-from-baseline in QTc interval. The QT interval was corrected for HR using the individual QT correction method (QTcI) as the primary QT correct method. QTcI coefficients were derived using all QT/RR data from the full 24-h Holter recording (all acceptable beats) on Day-1 of period 1. A negative TQT study – lack of clinically relevant QTc prolongation – was defined as the upper 95% single-sided confidence interval (CI) of the maximum baseline- and placebo-corrected QTc prolongation not exceeding 10 milliseconds.¹³

Secondary endpoints included change-from-baseline for HR, Fridericia's correction of QT (QTcF), the PR interval, and QRS duration (Δ HR, Δ QTcF, Δ PR, and Δ QRS). These parameters were used as the dependent variables for calculation of model-derived $\Delta\Delta$ HR, $\Delta\Delta$ QTcF, $\Delta\Delta$ PR, and $\Delta\Delta$ QRS for the by-timepoint analysis, respectively. The QTcF, which was used as the secondary QT correction method, is defined as $QTcF \text{ (millisecond)} = QT \text{ (millisecond)} / [RR \text{ (millisecond)} / 1000]^{1/3}$. Categorical outliers for QTcF ($QTcF > 450$ and ≤ 480 milliseconds, > 480 and ≤ 500 milliseconds, and > 500 milliseconds at any timepoint; increase of QTc from baseline > 30 and ≤ 60 milliseconds, and > 60 milliseconds), HR ($HR < 50$ bpm, $HR > 100$ bpm), PR ($PR > 200$ milliseconds), QRS ($QRS > 100$ milliseconds) intervals and changes in ECG morphology were also included as secondary endpoints. Assay sensitivity was demonstrated by showing that moxifloxacin produced a baseline- and placebo-corrected Change-from-baseline QTcI (Δ QTcI) prolongation with the lower bound of the one-sided 95% confidence interval (CI) > 5 ms at one or more timepoints between 1 and 4 h following dosing. The PK parameter used for PK analysis included area under the concentration-time curve (AUC) from time 0 to the last measurable concentration (AUC_{0-t}), $AUC_{0-\infty}$, T_{max} , C_{max} , V_{ss} , λ_z , $t_{1/2z}$ and plasma clearance (CL).

Safety endpoints included the incidence of AEs, serious adverse events (SAEs), changes in vital signs, physical examination, clinical laboratory evaluations, ECG parameters, observation of subject's consciousness, pregnancy test. Treatment-emergent adverse events (TEAEs) were defined as AEs that started on or after the first dosing or worsened in severity following dosing. All TEAEs, including those attributed to the study drug, were comprehensively catalogued by System Organ Class (SOC), Preferred Term (PT), and maximum severity. The severity grading was based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The CTCAE 5.0 severity grades were defined as follows: Grade 1 (Mild); Grade 2 (Moderate); Grade 3 (Severe); Grade 4 (Life-threatening); and Grade 5 (Death).

ECGs were obtained via 12-lead Holter monitors, which collected data on Day-1 of the first treatment period and on Day 1 of each treatment period (Day 1, Day 6, Day 11). ECGs were extracted in up to 10 replicates at the following timepoints: -60, -45, and -30 mins prior to dosing, and 1, 3, 5, 8, 10, 15, 30, 60 mins, and 2, 3, 4, 6, 10, and 24 h after dosing. For the PK analysis, blood samples were obtained from all subjects before dosing, and at 1, 2, 5, 10, 30, 60 mins and 2, 3, 6 h after dosing on Day 1 of each treatment period.

Sample Size

Assuming a one-sided 5% significance level and a within-participant standard deviation (SD) of 8 milliseconds for the Δ QTcI interval for all treatment groups and a true mean difference of 3 milliseconds in Δ QTcI interval between cipepofol and placebo, based on previous TQT study,¹⁶ a minimum sample size of 42 completed study subjects provided a power of 88% to demonstrate that the upper bound of all the two-sided 90% CIs on placebo-corrected Δ QTcI ($\Delta\Delta$ QTcI) interval would be below 10 milliseconds for up to 16 milliseconds post-dose time points. With these assumptions, a sample of 48 subjects was required to obtain at least 42 evaluable subjects who completed the study.

Statistical Analysis

The intention-to-treat (ITT) analysis set included all randomized subjects, which was used for analyses of demographic and baseline characteristics. The ECG analysis set (ECGS) was defined as all randomized subjects with a baseline ECG and at least one on-treatment ECG recording. The safety analysis set (SS) comprised all randomized subjects who received at least one study drug and underwent post-dose safety evaluations. The pharmacokinetic concentration analysis

set (PKCS) included all randomized subjects who had received cipepofol and had at least one valid plasma concentration measurement post-administration. The pharmacokinetic parameter analysis set (PKPS) was defined as all randomized subjects who received cipepofol and had at least one evaluable PK parameter without serious protocol violations, or without concomitant medications that had a significant impact on PK parameters.

Descriptive statistics were presented by treatment for all ECG parameters. Descriptive statistics with two-sided 90% confidence intervals (CIs, data-derived) were summarized for the change-from-baseline values at each timepoint by treatment group. The by-timepoint analysis for QTcI interval was based on a linear mixed-effects model with change-from-baseline QTcI (Δ QTcI) interval as the dependent variable, period, sequence, time, treatment, and time-by-treatment interaction as fixed effects, and baseline QTcI interval as a covariate. An unstructured covariance matrix was specified for the repeated measures at post-dose time points for participant within treatment period. The model also incorporated a participant-specific random effect on the intercept. The least squares (LS) mean, standard error (SE), and 2-sided 90% CI of Δ QTcI interval were calculated for comparison of “cipepofol versus placebo” and “moxifloxacin versus placebo” at each post-dose timepoint on Day-1. The ECG categorical outliers and morphological analysis were summarized using frequency tables, with counts and percentages.

Descriptive statistics for plasma concentrations were presented based on PKCS. Based on PKPS, PK parameters of cipepofol were summarized, including number of observations (N), mean $\pm$ standard deviation (SD), coefficient of variation (CV%), median (range), geometric mean (GM), geometric standard deviation (GSD) and geometric coefficient of variation (GCV%). All TEAE, changes in clinical laboratory parameters, physical examinations, and vital signs were summarized using descriptive statistics. All statistical analyses were performed using the SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Subject Disposition and Demographics

The subject disposition flow diagram is presented in Figure 2. Among the qualified 60 subjects, 12 backup subjects were enrolled but not randomized, as no replacements were required during the study period. All 48 randomized subjects

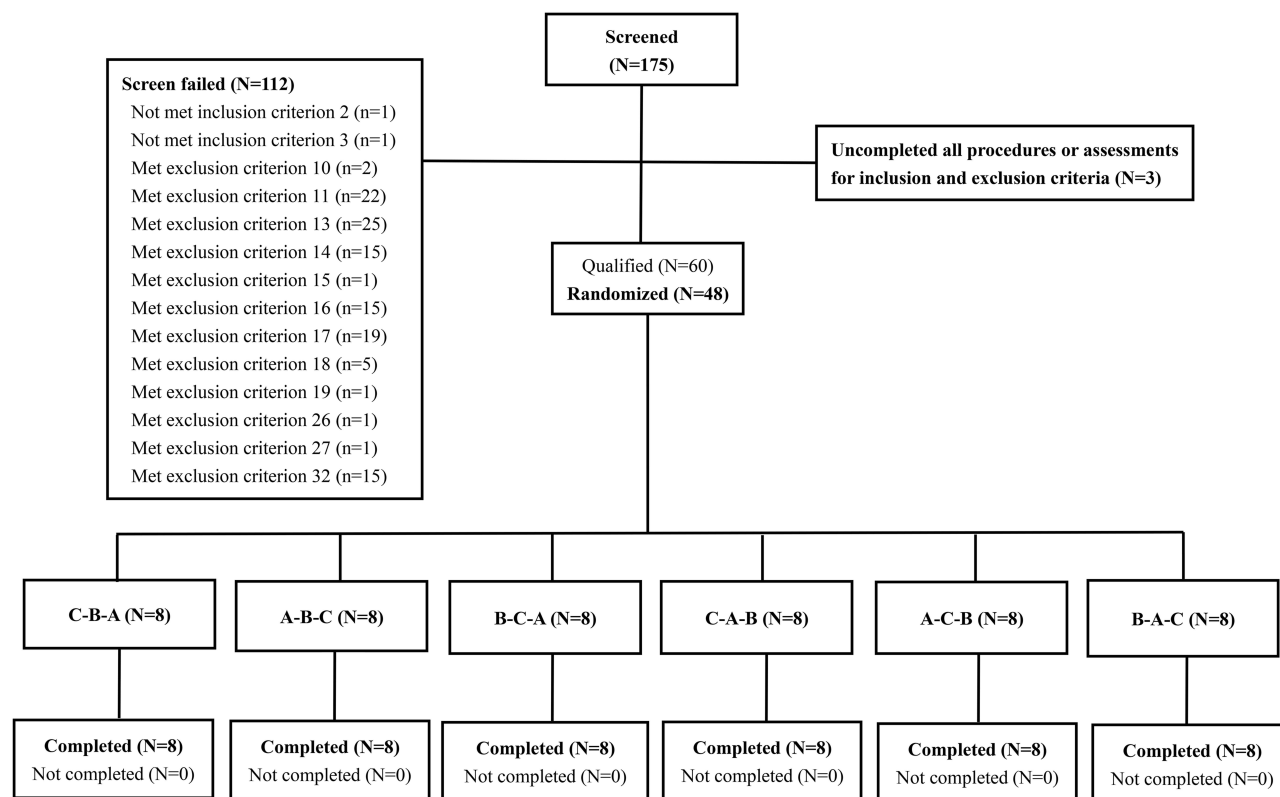


Figure 2 Subject flow diagram. (A) Placebo; (B) moxifloxacin; (C) cipepofol.

completed the study, forming the ITT analysis set. Among the randomized subjects, there were 40 males (83.3%) and 8 females (16.7%). The median (range) values for age, height, weight, and BMI were 31.5 (23–42) years, 168.90 (150.9–180.2) cm, 63.55 (45.7–75.1) kg, and 22.40 (20.2–25.7) kg/m², respectively. All 48 subjects were included in the ECGS and the SS. One subject was withdrawn from the PKCS and the PKPS due to an infusion pump failure in period 2, which impaired the administration of cipepofol. Consequently, 47 subjects were evaluable in the PKCS and the PKPS. Forty-eight subjects were randomized into 6 sequences, and the demographic characteristics were comparable across all the sequences. Detailed demographics and baseline characteristics are shown in [Table 1](#).

Outcomes and Estimation

Effect on HR

Upon administration of a 0.4 mg/kg IV bolus of cipepofol, a pronounced elevation in HR was noted during the initial 5–10 mins ([Figure 3A](#)). Specifically, the LS mean change from baseline HR (Δ HR) surged to 14.5 bpm within 1 min post-bolus, subsequently diminishing to below 10 bpm by 3 mins. Correspondingly, the LS mean placebo-corrected change in HR ($\Delta\Delta$ HR) peaked at 10.8 bpm 1 min post-dose and attenuated to 5.1 bpm by 10 mins post-dose ([Figure 3B](#)).

Effect on QTc Interval and Other ECG Parameters

Based on the ITT, no clinically significant effect on the QTcI interval was observed following IV bolus administration of cipepofol. The LS mean change-from-baseline QTcI (Δ QTcI) interval for cipepofol generally followed the pattern observed during the placebo treatment period across post-dose timepoints ([Figure 3C](#)). The LS mean placebo-corrected Δ QTcI ($\Delta\Delta$ QTcI) interval following cipepofol bolus ranged from –1.7 milliseconds (at 12 h post-dose) to 4.1 milliseconds (at 1 and 8 mins post-dose) ([Figure 3D](#)). Notably, the upper bound of the two-sided 90% CI for $\Delta\Delta$ QTcI interval was <10 milliseconds at all post-dose timepoints. Similar results were observed using the QTcF method ([Supplementary Figure S1](#)). Due to the expected effect of cipepofol on HR, a sensitivity analysis for the correction of QT/RR hysteresis was also performed. Using the weighted RR average methods, the upper bound of the two-sided 90% CI for $\Delta\Delta$ QTcI remained < 10 ms at all timepoints. Additionally, cipepofol had no clinically significant effects on PR and QRS intervals.

Categorical Outlier and Morphology Analyses

One subject in the 0.4 mg/kg treatment period and one subject in the placebo treatment period met the criteria for tachycardia outliers ([Table 2](#)). No subjects in the cipepofol treatment period developed a new QTcI interval >480 or an increase in QTcI interval from baseline >60 milliseconds. One subject in the cipepofol treatment period and 2 subjects in the moxifloxacin treatment period exhibited a new Δ QTcI interval > 30 and ≤ 60 milliseconds.

Table 1 Demographics and Baseline Characteristics of Study Subjects (Intention-to-Treat Population)

Variables	C-B-A N=8	A-B-C N=8	B-C-A N=8	C-A-B N=8	A-C-B N=8	B-A-C N=8	Total N=48
Age, Years	34.3 (4.77)	31.1 (4.94)	30.9 (3.56)	31.0 (5.76)	31.6 (5.26)	34.9 (5.00)	32.3 (4.94)
Gender, n (%)							
Male	6 (75.0)	6 (75.0)	7 (87.5)	7 (87.5)	8 (100)	6 (75.0)	40 (83.3)
Female	2 (25.0)	2 (25.0)	1 (12.5)	1 (12.5)	0	2 (25.0)	8 (16.7)
Ethnicity, n (%)							
Chinese-Han	8 (100)	7 (87.5)	8 (100)	8 (100)	8 (100)	7 (87.5)	46 (95.8)
Others	0	1 (12.5)	0	0	0	1 (12.5)	2 (4.2)
Height, cm	164.63 (7.107)	167.86 (8.973)	167.26 (5.190)	169.35 (5.721)	168.73 (5.708)	166.91 (9.702)	167.46 (7.043)
Weight, kg	61.78 (6.828)	64.46 (7.790)	64.16 (5.253)	61.06 (3.016)	67.09 (4.824)	63.54 (9.010)	63.68 (6.396)
BMI, kg/m ²	22.74 (0.964)	22.81 (2.017)	22.88 (1.429)	21.41 (0.777)	23.58 (1.296)	22.70 (1.977)	22.69 (1.546)
Work Status, n (%)							
Manual Labor	0	0	0	1 (12.5)	0	0	1 (2.1)
Non-manual Labor	8 (100)	8 (100)	8 (100)	7 (87.5)	8 (100)	8 (100)	47 (97.9)

Note: A, Placebo; B, moxifloxacin; C, cipepofol.
Abbreviation: BMI, body mass index.

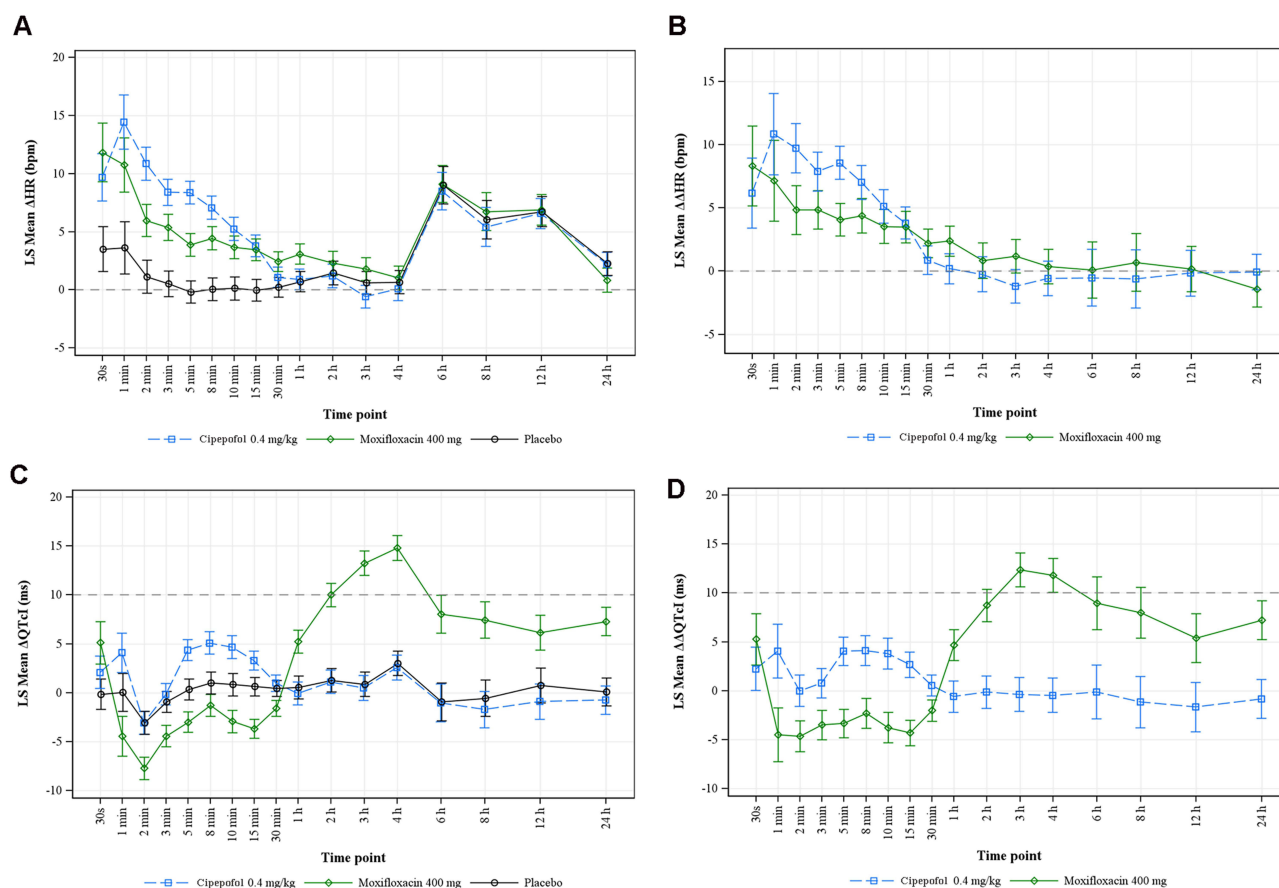


Figure 3 (A) Change-from-baseline HR (Δ HR) across timepoints with statistical modeling. (B) Placebo-corrected change-from-baseline HR ($\Delta\Delta$ HR) across timepoints with statistical modeling. (C) Change-from-baseline QTcI (Δ QTcI) across timepoints with statistical modeling. (D) Placebo-corrected change-from-baseline QTcI ($\Delta\Delta$ QTcI) across timepoints with statistical modeling.

Assay Sensitivity

In the moxifloxacin treatment sequence, the LS mean $\Delta\Delta$ QTcI interval reached a peak of 12.4 milliseconds (90% upper CI (UCI): 14.1 milliseconds) at 3 h post-dose (Table 3). The lower bound of the 90% CI exceeded 5 milliseconds at the 2, 3, and 4 h timepoints, thereby confirming assay sensitivity.

Pharmacokinetics Analysis

Based on PKCS and PKPS, the mean plasma concentration-time profile of cipepofol is depicted in Figure 4. PK parameters of cipepofol following a single IV bolus administration in healthy subjects are summarized in Table 4. The median (min, max) value of $T_{\max}$ for plasma cipepofol was 1.01 (0.55, 2.05) min. The GM value of $C_{\max}$, AUC_{0-t} , and $AUC_{0-\infty}$ for cipepofol were 2220 ng/mL, 231 h*ng/mL, and 251 h*ng/mL, respectively. The Mean $\pm$ SD value of $t_{1/2z}$ was 1.81 ± 0.431 h.

Safety Analysis

Based on the SS, six (6, 12.5%) subjects experienced nine AEs, of which, five (10.4%) subjects experienced grade 1 TEAEs and one (2.1%) subject experienced grade 2 TEAEs (Table 5). Among subjects who experienced TEAEs, three (6.3%) subjects experienced a total of five grade 1 TEAEs related to the investigational product. No serious adverse events (SAEs), TEAEs of grade ≥ 3 , or deaths were reported. Additionally, there were no TEAEs leading to dose reduction or interruption, study drug withdrawal, or study discontinuation. None of the AEs were associated with cardiac toxicity. Among the 48 subjects who received placebo, none experienced TEAEs. In contrast, three subjects who received cipepofol experienced four TEAEs, and three subjects who received moxifloxacin experienced 5 TEAEs.

Table 2 Categorical Outlier and ECG Morphologic Analyses

Variables	Cipepofol	Moxifloxacin	Placebo
Total, N	47	48	48
HR tachycardic outliers (HR increase from baseline >25% resulting in HR > 100 bpm, N (%))	1 (2.1%)	0	1 (2.1%)
Heart rate bradycardic outliers (HR decrease from baseline >25% resulting in HR < 50 bpm), N (%)	0	0	0
PR outliers (PR increase from baseline >25% resulting in PR > 200 ms), N (%)	0	0	0
QRS outliers (QRS increase from baseline >25% resulting in QRS > 100 ms), N (%)	0	0	0
QTcI > 450 and ≤ 480 ms	0	1 (2.1%)	0
QTcI > 480 and ≤ 500 ms	0	0	0
QTcI > 500 ms	0	0	0
ΔQTcI > 30 and ≤ 60 ms	1 (2.1%)	2 (4.2%)	0
ΔQTcI > 60 ms	0	0	0
QTcF > 450 and ≤ 480 ms	0	1 (2.1%)	0
QTcF > 480 and ≤ 500 ms	0	0	0
QTcF > 500 ms	0	0	0
ΔQTcF > 30 and ≤ 60 ms	2 (4.3%)	1 (2.1%)	0
ΔQTcF > 60 ms	0	0	0
2:1 AV Block	0	0	0
Atrial fibrillation	0	0	0
Atrial flutter	0	0	0
Complete left bundle branch block	0	0	0
Complete right bundle branch block	0	0	0
Mobitz I second degree AV block	0	0	0
Mobitz II second degree AV block	0	0	0
Myocardial infarction	0	0	0
Nonsustained VT	0	0	0
ST depression	0	0	0
ST elevation	0	1 (2.1%)	0
T-wave inverted	0	0	0
Third degree heart block	0	0	0
U-wave present	0	0	0

Note: PR was defined as time from the beginning of the P wave to the beginning of the next QRS. QRS: deflections in the tracing of the electrocardiogram comprising the Q, R, and S waves that represent depolarization of the ventricles complex.

Abbreviations: HR, heart rate; QTcI, individual QT correction; QTcF, Fridericia's correction of QT; AV, atrioventricular; VT, ventricular tachycardia.

Table 3 Assay Sensitivity Results Using by-Timepoint Analysis

Timepoint	Moxifloxacin 0.4g			
	LS Mean	I-Sided 95% CI Lower Bound	Adjusted Alpha	P value
1 h post-dose	4.7	3.09	0.05	0.6302
2 h post-dose	8.7	7.09	0.025	0.0001
3 h post-dose	12.4	10.66	0.0125	<0.0001
4 h post-dose	11.8	10.07	0.0167	<0.0001

Note: Based on a linear mixed-effects model: $\Delta\text{QTcI} = \text{Baseline QTcI} + \text{Treatment} + \text{Time} + \text{Time} \times \text{Treatment} + \text{Period} + \text{Sequence}$. An unstructured covariance structure was used to specify the repeated measures (at post-dose timepoints for participant within treatment period). The treatments and the timepoints having less than 3 observations were not included in the analysis. P value is I-sided test for $H_0: \Delta\Delta\text{QTcI} \leq 5$ milliseconds versus $H_1: \Delta\Delta\text{QTcI} > 5$ milliseconds.

Abbreviations: LS, least squares. CI, confidence interval.

Discussion

The present TQT study in healthy subjects demonstrates that cipepofol does not prolong the QTcI interval at the proposed therapeutic dose (0.4 mg/kg). Following cipepofol administration, a transient increase in HR was observed, which

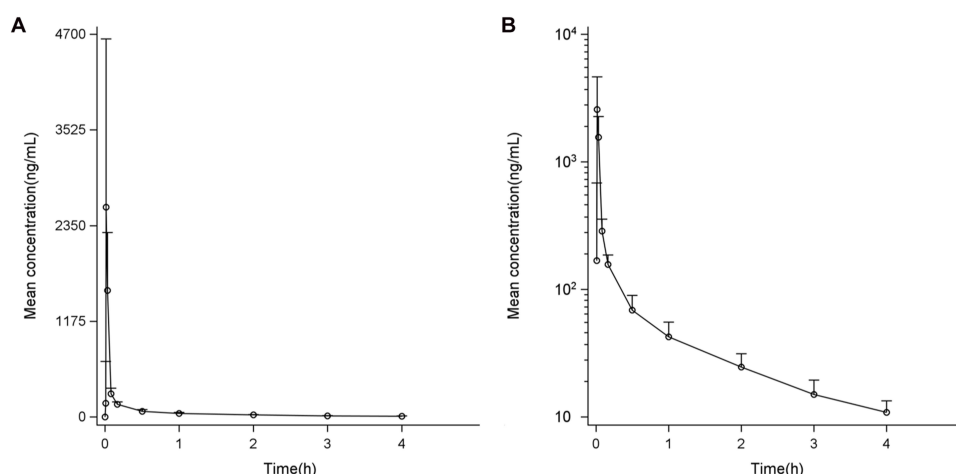


Figure 4 Mean plasma concentration-time plot of cipepofol. (A) Linear scale. (B) Logarithmic scale.

stabilized approximately 10 mins post-dose. This phenomenon, as previously reported, was commonly observed following administration of other IV anesthetics, such as propofol and remimazolam.^{8,17,18} To avoid the confounding influence of HR on QTc prolongation, subject-specific HR corrections (QTcI) were applied. The primary statistical endpoint was selected as the by-timepoint analysis rather than concentration-QTc (C-QTc) analysis due to the very rapid PK of cipepofol following bolus administration. Specifically, cipepofol achieved C_{max} very rapidly post-IV bolus and had a short half-life (the mean terminal elimination half-life of cipepofol in this study was 1.81 h). A sensitivity analysis was also performed to address the potential impact of QT/RR hysteresis associated with the rapid change in HR.

The LS mean placebo-corrected change-from-baseline in QTcI ($\Delta\Delta\text{QTcI}$) interval following cipepofol administration exhibited a maximum mean increase of 4.1 milliseconds at 12 h post-dose (when cipepofol exposure was minimal), and the upper bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcI}$ interval was <10 milliseconds at all post-dose timepoints. In the QT/RR hysteresis sensitivity analysis, the 90% upper CI for $\Delta\Delta\text{QTcI}$ using weighted RR averaging methods also

Table 4 Pharmacokinetic Parameters of Cipepofol

PK Parameters	N	Mean (SD)	Median (Range)	CV%	GM	GSD	GCV%
T_{max} (min)	47	1.33 (0.48)	1.01 (0.55–2.05)	36.4	1.23	1.41	35.4
C_{max} (ng/mL)	47	2790 (1890)	2150 (521–7960)	67.8	2220	2.02	79.9
AUC_{0-t} (h*ng/mL)	47	237 (55.3)	233 (128–399)	23.3	231	1.26	23.6
$AUC_{0-\infty}$ (h*ng/mL)	47	256 (54.9)	250 (141–423)	21.4	251	1.24	21.5
$AUC_{\%Extrap}$ (%)	47	7.82 (2.85)	7.24 (3.63–17.2)	36.4	7.36	1.42	36.3
R_{sq_a}	47	0.966 (0.031)	0.973 (0.895–1)	3.2	0.965	1.03	3.3
λ_z (1/h)	47	0.401 (0.0877)	0.381 (0.205–0.66)	21.9	0.392	1.25	22.6
$t_{1/2z}$ (h)	47	1.81 (0.431)	1.82 (1.05–3.39)	23.7	1.77	1.25	22.6
$MRT_{0-\infty}$ (h)	47	1.48 (0.378)	1.42 (0.914–2.62)	25.6	1.44	1.28	24.8
V_{ss} (L)	47	152 (49.5)	145 (75.4–288)	32.5	145	1.39	33.9
V_z (L)	47	266 (71)	264 (157–511)	26.7	257	1.29	26.3
CL (L/h)	47	102 (18.4)	101 (70.6–149)	18	101	1.2	18.3
V_z (L/kg)	47	4.19 (1.1)	4.04 (2.57–7.7)	26.3	4.06	1.29	25.9
CL (L/h/kg)	47	1.63 (0.357)	1.59 (0.94–2.83)	21.9	1.59	1.24	21.6

Abbreviations: PK, pharmacokinetic; SD, standard deviation; CV %, coefficient of variation; GM, geometric mean; GSD, geometric standard deviation; GCV %, geometric coefficient of variation; C_{max} , maximum plasma concentration; T_{max} , time to reach maximum plasma concentration; AUC_{0-t} , area under the concentration-time curve from time zero to the last measurable concentration; $AUC_{0-\infty}$, area under the concentration-time curve extrapolated to infinity; R_{sq_a} , coefficient of determination for the terminal phase (adjusted R-squared); $t_{1/2z}$, terminal elimination half-life; λ_z , elimination rate constant; $AUC_{\%Extrap}$, extrapolated area under the plasma concentration-time curve; $MRT_{0-\infty}$, mean residence time extrapolated to infinity; V_{ss} , volume of distribution at steady state; V_z , volume of distribution during the terminal phase; CL, total body clearance.

Table 5 Safety Assessments of Study Subjects

Variables	Placebo (N=48)		Moxifloxacin (N=48)		Cipepofol (N=48)		Total (N=48)	
	n (%)	Event	n (%)	Event	n (%)	Event	n (%)	Event
Any AE	0	0	3 (6.3)	5	3 (6.3)	4	6 (12.5)	9
Any TEAE	0	0	3 (6.3)	5	3 (6.3)	4	6 (12.5)	9
Investigations	0	0	2 (4.2)	3	3 (6.3)	4	5 (10.4)	7
Neutrophil count decreased	0	0	1 (2.1)	1	2 (4.2)	2	3 (6.3)	3
Alanine aminotransferase increased	0	0	0	0	1 (2.1)	1	1 (2.1)	1
Blood creatine phosphokinase increased	0	0	1 (2.1)	1	0	0	1 (2.1)	1
Blood thyroid stimulating hormone decreased	0	0	1 (2.1)	1	0	0	1 (2.1)	1
White blood cell counts decreased	0	0	0	0	1 (2.1)	1	1 (2.1)	1
Gastrointestinal disorders	0	0	1 (2.1)	1	0	0	1 (2.1)	1
Nausea	0	0	1 (2.1)	1	0	0	1 (2.1)	1
Nervous system disorders	0	0	1 (2.1)	1	0	0	1 (2.1)	1
Headache	0	0	1 (2.1)	1	0	0	1 (2.1)	1
Any TEAEs related to study product	0	0	1 (2.1)	2	2 (4.2)	3	3 (6.3)	5
Investigations	0	0	0	0	2 (4.2)	3	2 (4.2)	3
Neutrophil count decreased	0	0	0	0	1 (2.1)	1	1 (2.1)	1
Alanine aminotransferase increased	0	0	0	0	1 (2.1)	1	1 (2.1)	1
White blood cell counts decreased	0	0	0	0	1 (2.1)	1	1 (2.1)	1
Gastrointestinal disorders	0	0	1 (2.1)	1	0	0	1 (2.1)	1
Nausea	0	0	1 (2.1)	1	0	0	1 (2.1)	1
Nervous system disorders	0	0	1 (2.1)	1	0	0	1 (2.1)	1
Headache	0	0	1 (2.1)	1	0	0	1 (2.1)	1

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

remained <10 ms at all time points. The categorical and morphology analyses demonstrated that no subjects in the cipepofol treatment period developed a new QTcI > 480 or an increase in QTcI from baseline > 60 milliseconds. Additionally, cipepofol exerted no clinically significant effects on PR or QRS intervals, and no new clinically significant ECG morphologic findings were observed following cipepofol bolus administration. Assay sensitivity was successfully confirmed by the expected QTc interval prolongation following a 0.4 g dose of moxifloxacin. Based on these conditions, we conclude that a 0.4 mg/kg dose of cipepofol does not induce clinically significant QTc prolongation or other adverse clinical ECG effects.

The prolongation or abnormality of the QT interval observed in this study may be attributed to a spectrum of congenital and acquired factors that disrupt myocardial repolarization. Key considerations include genetic channelopathies, such as genetic mutation of the *Ikr*, *Iks* and *INA*, which underlie familial long QT syndromes.^{19–21} Acquired causes are frequently encountered and encompass several common categories: the use of QT-prolonging medications (eg, specific antibiotics, antiarrhythmics, and antipsychotics); electrolyte imbalances, particularly hypokalemia, hypocalcemia, and hypomagnesemia; and underlying systemic conditions including cardiac, neurological, or endocrine disorders.²⁰ Furthermore, contextual factors such as eating disorders (eg, anorexia nervosa) and hypothermia may also contribute.²² Differentiating among these etiologies is crucial for guiding appropriate clinical management.

This is the first prospective study to investigate the potential effects of cipepofol on cardiac repolarization in healthy subjects. Although QT-interval prolongation is acknowledged to be an imperfect biomarker for proarrhythmic risk, clinical assessments of drug-induced QT-interval prolongation remain a crucial component of overall proarrhythmic evaluation.¹⁰ As per the ICH E14 guideline, a TQT study is required to evaluate QTc interval changes at both therapeutic and suprathreshold dose levels of a new drug. However, in this study, a suprathreshold dose was not utilized due to safety concerns. Previous studies have demonstrated that many subjects required positive pressure ventilation when administered cipepofol doses of 0.6 mg/kg and above.²³ Therefore, suprathreshold exposure to cipepofol could not be

safely evaluated without additional ventilatory support or even intubation. Moreover, extra manual ventilatory support may also induce acute unintended changes in HR, blood pressure, and autonomic tone which could confound the interpretation of QTc interval data.

The PK profile of cipepofol indicated rapid absorption and distribution, as evidenced by a low median $T_{\max}$ of 1.01 min and $C_{\max}$ of 2150 ng/mL. The median $T_{\max}$ of cipepofol was consistent with the previously reported value.²⁴ Cipepofol demonstrated a relatively short $t_{1/2z}$ of 1.82 h, suggesting efficient elimination from the body. The low CV% values across the PK parameters, such as $C_{\max}$ (67.8%) and $AUC_{0-\infty}$ (21.4%), indicated good intersubject consistency in these parameters. These characteristics are crucial for evaluating the safety and efficacy of cipepofol and can guide optimal dosing regimens in future clinical trials. The findings align with the general understanding of PK, in which rapid absorption and distribution, along with efficient clearance, are desirable traits for drugs, particularly in the context of anesthesia, where quick onset and offset of action are beneficial.²⁵

In this study, the incidence of TEAEs (12.5%) was significantly lower than that reported in a Phase 1 study (NCT03745625) of cipepofol (75%) and a Phase 2 study (NCT04147416) of cipepofol (65.4%).^{5,8} These differences can primarily be attributed to variations in study designs, dosing sequences, cross-administrations, and study periods across these studies. Three subjects exhibited a total of five Grade 1 TEAEs, including elevated alanine aminotransferase, decreased neutrophil and white blood cell counts, nausea, and headache, which were initially attributed to the investigational product. These mild TEAEs were transient and resolved spontaneously within a few days without any medical intervention. Owing to the cross-administered study design, more detailed and thorough consideration was needed to determine whether these TEAEs were truly related to cipepofol. Furthermore, nausea and headache might be associated with moxifloxacin administration for the following reasons. First, nausea and headache are common AEs of moxifloxacin.^{26–28} Second, the two subjects who experienced nausea and headache only exhibited these symptoms following moxifloxacin administration. They did not experience these AEs following administration of either placebo or cipepofol during other study periods. Overall, a single IV bolus dose of 0.4 mg/kg cipepofol was found to be safe and well-tolerated in healthy subjects.

Several limitations of this study should be acknowledged. Firstly, the relatively small sample size might limit the generalizability of the findings and the statistical power to detect significant effects. Secondly, the gender distribution was imbalanced, with a higher proportion of male compared to female. However, this imbalance is unlikely to significantly impact the conclusions of the TQT study, as the primary endpoints and analyses are not inherently gender-specific.²⁹ Thirdly, the study sample lacked ethnic diversity, primarily comprising the Chinese-Han population. While this limits the external validity of the results across different ethnic populations, the core objectives of the TQT study are not directly influenced by ethnic differences in the context of the specific endpoints examined.³⁰ Fourthly, the study did not specifically exclude participants with cardiovascular diseases or account for the potential impact of such conditions (or their treatment) on outcomes. Future research should address these limitations by incorporating a larger and more diverse sample, balanced gender representation, and accounting for the potential influence of cardiovascular diseases.

Conclusion

In this study, cipepofol exhibited no clinically significant effects on QTc prolongation or other ECG parameters at the proposed therapeutic dose of 0.4 mg/kg IV bolus and was safe and well-tolerated in healthy subjects. Collectively, these findings support the further clinical development of cipepofol.

Data Sharing Statement

The dataset used and analyzed underlying this article is available from the corresponding author on reasonable request.

Ethics Approval Statement

Ethical approval was obtained from the Ethics Committee Institutional Review Board of Beijing Gobroad Boren Hospital (approval number: YW2024-003). All participants signed the informed consent form prior to study enrollment.

Consent for Publication

The subjects gave written informed consent for the publication of any associated data.

Acknowledgments

The authors thank the investigators at the participating site for their efforts and support. The authors also acknowledge the healthy volunteers participating in the study.

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.

Funding

The study was sponsored by Haisco-USA Pharmaceuticals, Inc.

Disclosure

M. Hu, P. Yan, and R. Zhou are employees of Haisco Pharmaceutical Group Co., and W. Daley is an employee of Haisco-USA. R. Kleiman and T. Rudo are the employees of Clario and have a consulting relationship with Haisco. J. Hou is the employee of Beijing Gobroad Boren Hospital, Beijing, China, and has a consulting relationship with Haisco. The authors report no other conflicts of interest in this work.

References

- Hung KC, Chen JY, Wu SC, et al. A systematic review and meta-analysis comparing the efficacy and safety of ciprofol (HSK3486) versus propofol for anesthetic induction and non-ICU sedation. *Front Pharmacol.* 2023;14:1225288. doi:10.3389/fphar.2023.1225288
- Wen J, Liu C, Ding X, et al. Efficacy and safety of ciprofol (HSK3486) for procedural sedation and anesthesia induction in surgical patients: a systematic review and meta-analysis. *Heliyon.* 2023;9(12):e22634. doi:10.1016/j.heliyon.2023.e22634
- Li X, Yang D, Li Q, et al. Safety, pharmacokinetics, and pharmacodynamics of a single Bolus of the γ -aminobutyric acid (GABA) receptor potentiator HSK3486 in healthy Chinese elderly and non-elderly. *Front Pharmacol.* 2021;12. doi:10.3389/fphar.2021.735700
- Bian Y, Zhang H, Ma S, et al. Mass balance, pharmacokinetics and pharmacodynamics of intravenous HSK3486, a novel anaesthetic, administered to healthy subjects. *Br J Clin Pharmacol.* 2020;87(1):93–105. doi:10.1111/bcp.14363
- Liu Y, Yu X, Zhu D, et al. Safety and efficacy of ciprofol vs. propofol for sedation in intensive care unit patients with mechanical ventilation: a multi-center, open label, randomized, phase 2 trial. *Chin Med J.* 2022;135(9):1043–1051. doi:10.1097/cm9.0000000000001912
- Luo Z, Tu H, Zhang X, et al. Efficacy and safety of HSK3486 for anesthesia/sedation in patients undergoing fiberoptic bronchoscopy: a multicenter, double-blind, propofol-controlled, randomized, phase 3 study. *CNS Drugs.* 2022;36(3):301–313. doi:10.1007/s40263-021-00890-1
- Gan TJ, Bertoch T, Habib AS, et al. Comparison of the efficacy of HSK3486 and propofol for induction of general anesthesia in adults: a multicenter, randomized, double-blind, controlled, phase 3 noninferiority trial. *Anesthesiology.* 2024;140(4):690–700. doi:10.1097/ALN.0000000000004886
- Hu C, Ou X, Teng Y, et al. Sedation effects produced by a ciprofol initial infusion or bolus dose followed by continuous maintenance infusion in healthy subjects: a phase 1 trial. *Advances in Therapy.* 2021;38(11):5484–5500. doi:10.1007/s12325-021-01914-4
- Lester RM. Update on ICH E14/S7B cardiac safety regulations: the expanded role of preclinical assays and the “double-negative” scenario. *Clin Pharmacol Drug Develop.* 2021;10(9):964–973. doi:10.1002/cpdd.1003
- Panicker GK, Kadam P, Chakraborty S, Kothari S, Turner JR, Karnad DR. Individual-specific QT interval correction for drugs with substantial heart rate effect using Holter ECGs extracted over a wide range of heart rates. *J Clin Pharmacol.* 2018;58(8):1013–1019. doi:10.1002/jcph.1258
- Goldenberg I, Mathew J, Moss AJ, et al. Corrected QT variability in serial electrocardiograms in long QT syndrome: the importance of the maximum corrected QT for risk stratification. *J Am Coll Cardiol.* 2006;48(5):1047–1052. doi:10.1016/j.jacc.2006.06.033
- Abriach VA, Ramakrishna H, Mehta A, Mookadam F, Srivathsan K. The possible role of propofol in drug-induced torsades de pointes: a real-world single-center analysis. *Int J Cardiol.* 2017;232:243–246. doi:10.1016/j.ijcard.2017.01.011
- Industry Gf. E14: clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. *FDA*; 2005.
- Lee J, Lester R, O'Reilly T, et al. A randomized, double-blind, parallel design thorough QT study with a nested crossover to compare the cardiac safety of amiselimod with placebo and positive control in healthy volunteers. *Clin Pharmacol Drug Develop.* 2023;12(3):236–248. doi:10.1002/cpdd.1210
- Lester RM, Paglialunga S, Johnson IA. QT assessment in early drug development: the long and the short of it. *Int J Mol Sci.* 2019;20(6):1324. doi:10.3390/ijms20061324
- Zhang J, Machado SG. Statistical issues including design and sample size calculation in thorough QT/QTc studies. *Journal of Biopharmaceutical Statistics.* 2008;18(3):451–467. doi:10.1080/10543400802020938

17. Kleiman RB, Darpo B, Thorn M, Stoehr T, Schippers F. Potential strategy for assessing QT/QTc interval for drugs that produce rapid changes in heart rate: electrocardiographic assessment of the effects of intravenous remimazolam on cardiac repolarization. *Br J Clin Pharmacol.* **2020**;86(8):1600–1609. doi:10.1111/bcp.14270
18. McKeage K, Perry CM. Propofol: a review of its use in intensive care sedation of adults. *CNS Drugs.* **2003**;17(4):235–272. doi:10.2165/00023210-200317040-00003
19. van Noord C, Eijgelsheim M, Stricker BH. Drug- and non-drug-associated QT interval prolongation. *Br J Clin Pharmacol.* **2010**;70(1):16–23. doi:10.1111/j.1365-2125.2010.03660.x
20. Gotta V, Donner B. QT interval prolongation: clinical assessment, risk factors and quantitative pharmacological considerations. *J Pharmacokinetic Pharmacodyn.* **2025**;52(6):61. doi:10.1007/s10928-025-10010-x
21. Ranganathan D, Grondin S, Hadjeres R, Joza J. Congenital long QT syndrome: a focus on risk stratification and management. *Rev Cardiovasc Med.* **2025**;26(6):36779. doi:10.31083/rm36779
22. Rani S, Agstam S. Shall we stop focusing on QTc interval in eating disorders? *Am J Med.* **2021**;134(1):e72. doi:10.1016/j.amjmed.2020.04.021
23. Teng Y, Ou MC, Wang X, et al. Pharmacokinetic and pharmacodynamic properties of ciprofol emulsion in Chinese subjects: a single center, open-label, single-arm dose-escalation phase 1 study. *Am J Transl Res.* **2021**;13(12):13791–13802.
24. Yang D, Zhang W, Ruan Z, et al. Drug-drug interaction study of ciprofol and sodium divalproex: pharmacokinetics, pharmacodynamics, and safety in healthy Chinese subjects. *Clin Transl Sci.* **2023**;16(10):1972–1981. doi:10.1111/cts.13605
25. Billard V. Pharmacokinetic-pharmacodynamic relationship of anesthetic drugs: from modeling to clinical use. *F1000Research.* **2015**;4:1289. doi:10.12688/f1000research.6601.1
26. Li Y, Zhu D, Peng Y, et al. A randomized, controlled, multicenter clinical trial to evaluate the efficacy and safety of oral sitafloxacin versus moxifloxacin in adult patients with community-acquired pneumonia. *Curr Med Res Opin.* **2021**;37(4):693–701. doi:10.1080/03007995.2021.1885362
27. DeAbate CA, Mathew CP, Warner JH, Heyd A, Church D. The safety and efficacy of short course (5-day) moxifloxacin vs. azithromycin in the treatment of patients with acute exacerbation of chronic bronchitis. *Respir Med.* **2000**;94(11):1029–1037. doi:10.1053/rmed.2000.0927
28. Kelleher D, Tombs L, Preece A, Brealey N, Mehta R. A randomized, placebo- and moxifloxacin-controlled thorough QT study of umecclidinium monotherapy and umecclidinium/vilanterol combination in healthy subjects. *Pulm Pharmacol Ther.* **2014**;29(1):49–57. doi:10.1016/j.pupt.2014.07.002
29. Macfarlane PW, McLaughlin SC, Devine B, Yang TF. Effects of age, sex, and race on ECG interval measurements. *J Electrocardiol.* **1994**;27(Suppl):14–19. doi:10.1016/s0022-0736(94)80039-1
30. Mansi IA, Nash IS. Ethnic differences in electrocardiographic intervals and axes. *J Electrocardiol.* **2001**;34(4):303–307. doi:10.1054/jelc.2001.27453

Drug Design, Development and Therapy

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/drug-design-development-and-therapy-journal>

Dovepress
Taylor & Francis Group