The safety, toleration, and pharmacokinetics comparison of two intravenous voriconazole formulations in healthy Chinese volunteers after three ascending doses

Gang Chen[1], Zejuan Wang[2], Xiaona Liu[2], Yanan Zhang[2], Min Li[2], Aihua Du[2], Haiqing Zhen[3], Xiaolin Wang[2], Dan Zhang[2], Mengke Zhang[2], Siqi Zang[2], LIna Zhang[2], Xueyan Li[2], Huiting Zhu[2], and Jin Wang[2]

[1]Affiliation not available
[2]Aerospace Center Hospital
[3]Aerospace Center Hospita

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Abstract

Objectives To evaluate the safety, toleration, and pharmacokinetics (PKs) comparison of two intravenous voriconazole formulations after three ascending dose administrations in healthy Chinese subjects. Methods A randomized, double-blind, placebo- and positive-controlled trial was conducted in three cohorts with a total of 42 healthy Chinese subjects. Every cohort of 14 subjects was allocated in proportion (8:4:2) to test formulation, positive voriconazole or placebo successively by single first and then multiple dose administration of 3 mg/kg, 4 mg/kg, and 6 mg/kg. Key findings A total of 41 subjects completed all drug administrations. The pharmacokinetics of test formulations are characterized by high interindividual variability with a coefficient of variance of Cmax up to 67.95% and AUC0-τ up to 70.16% and nonlinear pharmacokinetics with a regression coefficient of Cmax of 1.31 and AUC0-τ of 1.75 in a single dose. In the steady state, RAuc (mean±SD) of test drug vs positive control drug of 3 mg/kg, 4 mg/kg, and 6 mg/kg dose group was 5.18±1.07 and 5.26±0.99, 5.59±1.15 and 6.27±0.58, and 5.82±0.47 and 5.52±0.76, respectively; and Rcmax (mean±SD) were 2.50±0.44 and 2.68±0.72, 2.63±0.46 and 3.11±0.57, and 2.79±0.28 and 2.55±0.34, respectively. Adverse events with 37 transient visual disturbances were mainly mild. Conclusions The pharmacokinetics with high interindividual variability, nonlinear characteristics and significant dose-dependent accumulation were comparable in the two formulations. The overall safety of the test formulation was tolerable.

1 Introduction

Voriconazole, available in intravenous, tablet, and oral suspension forms, is a new-generation triazole antifungal agent with potent activity against a broad spectrum of clinically significant pathogens, including Aspergillus, Cryptococcus, and Candida species[1,2]. It is an antifungal medicine that is used to treat infections and the first-line treatment agent for invasive aspergillosis (IA), serious Candida infections, and infections caused by Scedosporium species and Fusarium species, as indicated by the United States Food and Drug Administration (FDA)[3], as recommended by the Infectious Diseases Society of America guidelines in 2008[4]. At plasma concentrations, voriconazole is known to demonstrate highly variable, nonlinear pharmacokinetic characteristics related to the polymorphic drug-metabolizing enzyme CYP2C19 and adverse events (AEs)[5-8]. Wide intraindividual and interindividual variability has been reported for voriconazole plasma concentrations in healthy subjects[9]. Several factors impact this variability, including genetic polymorphisms of the CYP2C19 enzyme, liver disease, drug–drug interactions, and age[10,11].

Although the clinical pharmacokinetics of voriconazole following i.v. dosing have been well characterized,

many hospitalized critical patients require treatment with an intravenous regimen initially, followed by a continuous regimen by b.i.d. for 5 days. Owing to the large variability of plasma exposure and the wide clinical applications of voriconazole for injection, adverse reactions include visual impairment, fever, rash, vomiting, nausea, diarrhea, headache, peripheral edema, abnormal liver function test, respiratory distress, and abdominal pain[12,13].

In addition, for voriconazole injection, the price of the original drug is approximately three times greater than that of the domestic generic drug. Therefore, there is a need to reduce the economic burden on individuals, families, and society and improve drug accessibility for patients. For the development of voriconazole injections, the toxicity of the excipient accumulation of Betadex sulfobutyl ether sodium and sulfobutyl ether-beta-cyclodextrin sodium salt (SBECD) is also a concern. As declared by the Center for Drug Evaluation (CDE), NMPA (CYHS1900527), the SBECD excipients of generic test formulations, need to be tested to evaluate the safety, tolerability, and pharmacokinetics of test formulations compared with original drugs. To this end, a blinded, randomized, controlled, single-, and multiple-dose study was conducted in this study after the intravenous administration of voriconazole [Center for Drug Evaluation (CDE) identifier: CTR20201060.].

2 Materials and Methods

2.1 Participants and formulations

A total of 42 healthy Chinese male and female volunteers (sex ratio, 1:1) aged 18-45 years, weighing 45 (female) or 50 (male) to 75 kg with a body mass index of 19-26 according to Quetelet's index [weight (kg)/height^2 (m)] were enrolled in this study. Volunteers with any physical or laboratory abnormalities, abnormal chest imaging and ophthalmic examination, a history of clinically significant disease (especially drug sensitivity) in response to medical treatment, or a history of clinically significant visual impairment (e.g., vision, visual field, or color abnormality) were excluded.

The test formulation (voriconazole injection, 0.2 g, lot no. PFL180101 with a voriconazole content of 100.5% and expiration date in December 2020) and placebo formulation (lot no. PFLK200501 with expiration date in April 2021) used in this study were obtained from Suzhou Borui Pharmaceutical Co., Ltd. (Suzhou, Jiangsu, China). The reference formulation (Vfend®, 0.2 g, lot no. Z594801 with a voriconazole content of 104.1% and expiration date in December 2021) was produced by Pharmacia & Upjohn Company.

2.2 Study design

This randomized, placebo-controlled, positive-controlled, parallel-group, double-blinded study was approved on May 21, 2020 by the Ethics Committee of the Aerospace Center Hospital (No: EC2020-16). Among 42 subjects, every 14 subjects enrolled in the study were successively assigned to one of three escalation cohorts (3 mg/kg, 4 mg/kg, and 6 mg/kg) when the tolerability assessment for previous administration was good. The subjects of each cohort were randomized 4:2:1 to test formulation, positive control, or placebo. Each subject was administered one single dose (day 1), followed by multiple doses (on days 4-8) every 12 h i.v. for nine doses after three-day washout (Table 1).

2.3 PK assessment

Venous blood samples (sufficient to provide 0.8 ml of plasma) were collected in 3 ml EDTA tubes at the PK collection times shown in Table 1. In the cohort of 3 mg/kg and 4 mg/kg, sampling was conducted predose and at frequent intervals (on day 1 and day 8) until 216 hours postdose. For the 6 mg/kg, the additional sample at the 240 h、264 h and 288 h post-dose were collected after the last dose. Plasma was separated by centrifugation (2500 g for 10 min at 4°C) and stored immediately at -80°C until analysis.

The plasma concentrations of voriconazole were quantified by LC–MS/MS. Liquid chromatography was performed on an ExionLCTM UHPLC system (SCIEX) with a Venusil MP C18 column (50 mm×2.1 mm, 5.0 μm; Agela Technologies). An API 4000 triple quadruple mass spectrometer equipped with an electrospray ionization (ESI) source (SCIEX) was used for mass spectrometric detection. The quantitative analysis of

voriconazole and IS in human plasma was performed in multiple reaction monitoring (MRM) mode. The detection method was fully validated according to US FDA guidelines. The lower limit of quantification (LLOQ) was 15.0 ng/mL, and the method was linear in the concentration range of 15.0–15000 ng/mL.

2.4 Pharmacokinetic parameters

Individual PK parameters were calculated by a noncompartmental method using WinNonlin 8.3.1. The maximum observed plasma concentration (C_{max}), the plasma concentration immediately before the following dose (C_{trough}), and the time to achieve C_{max} (T_{max}) were determined by directly inspecting the individual plasma concentration–time profiles. The area under the plasma concentration–time curve (AUC) from dosing to the time of the last quantifiable concentration ($AUC_{0\text{-last}}$) and the AUC up to the time point of the next dosing (12 h) ($AUC_{0\text{-}\tau}$) were calculated using the linear-up/log-down trapezoidal method. The terminal elimination constant (λz) was estimated from the natural logarithmic-transformed plasma concentration–time curve using linear regression, and the terminal elimination half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda z$. The AUC from dosing to time infinity (AUC_{inf}) was determined using $AUC_{0\text{-last}}$ + C last/λ_z.

Multiple-dose pharmacokinetics include more parameters in addition to those described above. The average steady-state plasma concentration (Cav, ss) was calculated as $AUC_{0\text{-}\tau}$, ss/τ, where $AUC_{0\text{-}\tau}$, ss is the AUC in a dosing interval at steady state, which is calculated from 0 to τ h post-dose on Day 8, and τ is the dosing interval (12 h). The minimum plasma concentration (Cmin, ss) is the plasma concentration predose on day 8. The degree of fluctuation (DF) was determined as (Cmax, ss–Cmin, ss)/Cav, ss. The accumulation ratio (R_{AUC}) was calculated from $AUC_{0\text{-}\tau}/AUC_{0\text{-}12}$, where $AUC_{0\text{-}12}$ is the AUC calculated from 0 to 12 h postdose on Day 1.

2.5 Safety and tolerability assessments

All adverse events (including SAE) that occurred during the trial were recorded, particularly the time of onset, duration, and severity, and their relationship to treatment according to the assessment. City Universal Color Test (2nd ed.) (color vision), Snellen chart (visual acuity), and evaluation of visual impairment observation and follow-up were used to assess visual disturbance during or after drug infusion based on the common adverse reactions to voriconazole. In addition, routine blood and urine tests and clinical chemistry tests (including liver function) were performed at screening, baseline, before the morning dose on days 9 and 11, withdrawal visit, and follow-up visit. Depending on the symptoms and signs during the infusion, further clinical chemistry tests were performed. A 12-lead electrocardiogram was performed once at 2 h after the morning dose infusion when screening, at baseline, at day 9, at day 11, and at the withdrawal visit. If ECG was abnormal with clinical significance, it was performed twice at least 1-minute intervals. Vital signs were measured throughout the study, including at screening, baseline, 1 h prior to the morning dose, 2 h and 8 h after the morning dose on days 1 to 8, 1 h prior to the evening dose, 2 h after the evening dose on days 4 to 7, and 8:00-10:00 am and 20:00-22:00 pm on days 2, 3, 9 and 10.

2.6 Statistical analysis

Statistical analysis of the demographics of the subjects and safety was performed using SAS V9.4 (SAS Institute Inc., Cary, NC, USA). The software package Phoenix WinNonlin 8.3 was used to analyze the pharmacokinetic parameters of the test and reference formulation without a placebo group using descriptive statistics (mean, SD, medium, CV, min, and max). A pharmacokinetic analysis of the plasma concentration data was conducted using a nonlinear mixed-effects modeling approach. The power model was used to evaluate the linear relationship between AUC, C_{max}, and the dose of voriconazole in plasma, as well as dose-proportional analysis between the single-dose and multiple-dose studies.

The AUC_{inf}, $AUC_{0\text{-}t}$, and C_{max} of voriconazole for the single-dose administration and AUC_{tau} and $C_{max,ss}$ of voriconazole for the multiple-dose administration were analyzed for dose proportionality using a power model. The following model was fitted: log e (AUC or C_{max}) = μ + β*log e (dose). The estimation obtained for β was a measure of the dose proportionality, which was assessed separately for Chinese subjects. No formal statistical inference was performed for the β estimate. This model was fitted with a simple linear regression

(using SAS PROC REG) to estimate the slope of the regression line and a two-sided 95% confidence interval (CI) for the slope coefficient β. The estimated values of the slope close to 1 are considered evidence of dose proportionality.

3 Results

3.1 Participants

A total of 42 subjects were enrolled with a 1:1 sex ratio. These subjects were enrolled into three cohorts (3 mg/kg, 4 mg/kg, and 6 mg/kg) (n=14). The demographic characteristics of the 42 subjects in the three cohorts are shown in Table 2. There were no significant differences in age, height, weight, or BMI among the groups. All subjects completed the study, except for one individual who withdrew from the 3 mg/kg cohort on day 4 after the morning infusion of multiple doses as a result of an abnormality in the 12-lead electrocardiogram. All subjects were included in the safety evaluation, and all subjects who received the test formulation of voriconazole or the positive voriconazole were included in the pharmacokinetic analysis.

3.2 Safety and tolerability

One subject (female) dropped out from the study due to a multifocal ventricular premature heartbeat observed in the 2 h ECG after the first morning dose infusion of multiple doses compared with the baseline ECG in the 3 mg/kg cohort. After her withdrawal, a follow-up ECG showed that the multifocal ventricular premature heartbeat had disappeared. Investigators considered it unlikely to be drug-related based on the subject's past medical history of premature beat but without true disclosure to the investigator at that time during screening. All thirty-six of the subjects receiving voriconazole and six subjects in the placebo group experienced 83 treatment-emergent adverse events (TEAEs) (table 3). Among them, in the highest-dose regimen (6 mg/kg), one subject experienced a severe rash in Grade 3, three subjects experienced five moderate adverse reactions in Grade 2 (two serum aspartate aminotransferase (AST) elevation, one alanine aminotransferase (ALT) elevation, and one dizziness and one ear stuffiness). Other adverse events were associated with laboratory tests, ECG, hallucinations, insomnia, and visual disturbance; however, all were mild in Grade 1 without SAE. All 35 mild visual disturbances, including 8 flash hallucinations, 13 yellow vision, 8 photophobia, 6 blurred vision, and 1 green vision, were spontaneously reported by a total of nine subjects administered voriconazole. All 41 subjects were generally well tolerated at 10 or 13 days during the SAD and MAD studies.

3.3 Pharmacokinetics

The mean plasma concentration-time profiles of the test and positive voriconazole in the subjects of the three cohorts after the SAD and MAD study are displayed in Fig. 1 (3 mg/kg), Fig. 2 (4 mg/kg), and Fig. 3 (6 mg/kg). The main pharmacokinetic parameters are summarized in Tables 4 and 5.

In the SAD study, the median T_{max} was 2 h for the test drug and positive drug with different doses of 3 mg/kg, 4 mg/kg, and 6 mg/kg. The average range of $T_{1/2}$ was 5.91˜7.74 h and 6.85˜9.48 h for the test drug and positive drug with a dose of 3˜6 mg/kg, respectively, with slight differences between the two drugs. The C_{max}, AUC_{0-t}, and $AUC_{0-[?]}$ of the test and positive voriconazole were 1395.00 ± 226.21 and 1312.50±188.39 ng/mL, 5882.41±2504.46 and 6973.43±4738.70 h*ng/mL, and 6307.86 ± 2962.08 and 7325.64 ± 5139.63 h*ng/mL at 3 mg/kg, respectively; 2001.25 ± 314.48 and 2162.50 ± 400.53 ng/mL, 10569.15 ± 6747.11 and 14283.35 ± 7439.36 h*ng/mL, 11204.44 ± 7550.59 and 15505.65 ± 8539.06 h*ng/mL at 4 mg/kg, respectively; and 3461.25 ± 558.99 and 3177.50 ± 736.13 ng/mL, 19050.06 ± 4201.76 and 13968.63 ± 3998.84 h*ng/mL, 19723.31 ± 4073.39 and 14938.04 ± 4144.66 h*ng/mL at 6 mg/kg, respectively.

In the MAD study with different doses of 3 mg/kg, 4 mg/kg, and 6 mg/kg, test and positive drugs were administered intravenously nine times, q12 h from day 4 to day 7, and once in the morning of day 8. On day 4 and 5, both drugs reached steady state. The average T_{max} in the steady state was 170.00 h for the two drugs. The C_{max}, AUC_{0-t}, and $AUC_{0-[?]}$ of the test and positive voriconazole was 3550.00 +- 891.87 and 3547.50 +- 1166.37 ng/mL, 26943.86 +- 10174.67 and 27631.88 +- 12678.71 h*ng/mL, and 63950.38 +- 45110.55 and 83980.04 +- 95273.34 h*ng/mL at 3 mg/kg, respectively; 5337.50 +- 1626.23 and 6807.50

+- 1920.70 ng/mL, 43572.63 +- 19885.07 and 59226.25 +- 21102.34 h*ng/mL, and 178049.94 +- 222943.05 and 268193.50 +- 168709.02 h*ng/mL at 4 mg/kg, respectively; and 9617.50 +- 1545.01 and 8090.00 +- 2101.82 ng/mL, 43572.63 +- 19885.07 and 59226.25 +- 21102.34 h*ng/mL, and 272017.81 +- 63103.68 and 166054.79 +- 93499.64 h*ng/mL at 6 mg/kg, respectively.

In the steady state after multiple administration, RAuc (mean+-SD)of test drug vs positive control drug of 3 mg/kg, 4 mg/kg, and 6 mg/kg was 5.18 +- 1.07 and5.26 +- 0.99, 5.59 +- 1.15 and 6.27 +- 0.58, and5.82 +- 0.47and 5.52 +- 0.76, respectively; and Rc_{max} (mean +- SD) were 2.50 +- 0.44 and 2.68 +- 0.72, 2.63 +- 0.46 and 3.11 +- 0.57,and 2.79 +- 0.28 and 2.55 +- 0.34, respectively.

For the test intravenous voriconazole, a 2-fold increase in the single dose from 3 mg/kg to 6 mg/kg resulted in a 2.5- and 3.2-fold increase in C_{max} and $AUC_{0\text{-}t}$, respectively. The pharmacokinetics of the test intravenous voriconazole are characterized by high interindividual variability with a coefficient of variance of Cmax up to 67.95% and $AUC_{0\text{-}\tau}$ up to 70.16% at a single dose and nonlinear pharmacokinetics with a regression coefficient of Cmax of 1.31 and $AUC_{0\text{-}\tau}$ of 1.75 at a single dose and Cmax of 1.39 and $AUC_{0\text{-}\tau}$ of 1.57 at multiple doses. There was a greater proportion of drug exposure increase than dose increase.

4 Discussion

The safety, toleration, and pharmacokinetics of intravenous voriconazole in healthy Chinese subjects were evaluated in three cohorts of different dose regimens after SAD and MAD administration at 3 mg/kg, 4 mg/kg, and 6 mg/kg. A total of 42 healthy subjects were enrolled in this study, 41 of whom completed all the drug administration tests according to the requirements of the scheme; one subject was withdrawn due to an AE after completing a single dose of PK.

In general, this pharmacokinetic study showed high intersubject variability. As a consequence of this high variability, different patients treated with voriconazole at the same dose can exhibit a wide range of drug concentrations in their plasma. The results of this study showed that voriconazole exhibits nonlinear pharmacokinetics in healthy Chinese adults, which is consistent with the original voriconazole. This nonlinearity may be due to saturable systemic clearance (CL)[9]. In a single intravenous infusion, the PK parameters of different doses were essentially the same, with a consistent trend of dose escalation between the test drug and the positive drug.

After multiple doses of voriconazole were administered, in each dose cohort, significant accumulation of voriconazole in plasma was observed in the body of the subjects for the test drug and the positive-controlled drug voriconazole due to the nonlinear phamacokinetics. It showed a steady state on day 8 (D8) with significant dose-dependent accumulation and decreased systemic CL, showing a slightly increasing trend with increasing dose, with no significant difference in this study for either the test drug or positive drug. The accumulation index of R_{AUC} and Rc_{max} in the test formulation group increased slightly with an increase in the dose. An atypical linear relationship was observed between single-dose and multiple-dose studies. Exposure, in terms of peak plasma concentration (C_{max}) and AUC, increased in a disproportionate manner with dosage. The proportion of increased drug exposure was greater than that of the increased dose.

For the test formulations, a 2-fold increase in the single dose from 3 mg/kg to 6 mg/kg resulted in a 2.5- and 3.2-fold increase in C_{max} and $AUC_{0\text{-}t}$, respectively. After multiple dosing with 3 mg/kg IV bid, the C_{max} and $AUC_{0\text{-}t}$ values increased approximately 2.5- and 4.5-fold, respectively, after a single dosing, which was similar to 4 mg/kg and 6 mg/kg, respectively. In general, these pharmacokinetic studies showed high intersubject variability in the estimates of $C_{max}$and AUC following SAD and MAD studies. Intersubject variability (expressed as CV %) ranged from approximately 15% to greater than 100%.

The AEs of the test drug and positive drug groups increased with an increase in dose. Multiple doses of voriconazole were well tolerated in these studies, and no serious adverse events were observed. The main AEs, such as elevated aspartate aminotransferase, insomnia, elevated alanine aminotransferase, flash hallucination, yellow vision, photophobia, blurred vision, vertigo, decreased serum potassium, and prolonged QT interval of ECG, all reported adverse reactions according to the instructions for positive-controlled drugs.

In this study, the most frequent TEAEs of voriconazole were transient visual disturbances without structural or functional sequelae. None of the subjects discontinued the study due to visual adverse events. Several studies of voriconazole have shown that the most distinctive visual reaction to the drug is an altered or enhanced perception of light[7,14-17]. Other reactions have included blurred vision, color vision change, and photophobia[18]. The visual reactions observed in this study were similar to those previously reported and were all classified as mild in nature, transient, and spontaneously resolved[19].

In summary, the pharmacokinetic parameters of healthy Chinese volunteers showed nonlinear characteristics after single and multiple intravenous infusions of different doses of voriconazole (3 mg/kg, 4 mg/kg and 6 mg/kg). Significant dose-dependent accumulation in the bodies of the subjects was observed after repeated administration in each cohort. The accumulation index R_{AUC} and R_{Cmax}increased slightly with an increase in the dose. Adverse events were mainly mild (grade 1), and the main drug-related AEs in the study were expected. The frequency of AE increased with an increase in dose. The overall safety was tolerable. In conclusion, the pharmacokinetics, safety, and tolerability of test voriconazole were comparable to those of Vfend® after SAD and MAD intravenous infusion. The generic test voriconazole can be further verified as a clinically effective alternative to Vfend® in a bioequivalent study in healthy Chinese adults.

COMPETING INTERESTS

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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CONTRIBUTORS

G.C., Z.W., X.L.,H.Z.and J.W. contributed to the study design and protocol. Z.W.,G.C, X.L.,Y.Z., M.L., A.D, H.Z., M.Z., X.W., D.Z., S.Z., L.Z. and X.L. conducted the study. G.C.and Z.W.analysed/interpreted the data, critically revised the manuscript.All authors agreed on the content, and J.W. approved the finalversion for publication.

DATA AVAILABILITY STATEMENT

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

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Figure and Table legends

FIGURE 1 . Mean (standard error) plasma voriconazole concentration-time profiles between the test product (test: T) and the positive comparator (reference: R) in the 3 mg/kg cohort

FIGURE 2 . Mean (standard error) plasma voriconazole concentration-time profiles between the test product (test: T) and the positive comparator (reference: R) in the 4 mg/kg cohort

FIGURE 3 . Mean (standard error) plasma voriconazole concentration-time profiles between the test product (test: T) and the positive comparator (reference: R) in the 6 mg/kg cohort

TABLE 1 Dosing regimens* and PK* collection time

Cohort(n)	Group (n)	Dose on day 1(i.v.)	Dose on day 1-3*	Dose on day 4-7(i.v.)	Dose on day 6-7*	Dose on day 6-7*	Dose on day 8(i.v.)	Dose on day 8(i.v.)	Do da 8-1 13

1(14)	Test drug(8) Positive drug(4) Placebo(2)	3 mg/kg q.d.	PK(time):-1 h (predose)、0.5 h、1 h、1.5 h、2 h(end time)、2.5 h、3 h、4 h、6 h、8 h、12 h、24 h and 48 h	3 mg/kg b.i.d.	3 mg/kg b.i.d.	PK(time): -1 h(predose) and 2 h (end time)	PK(time): -1 h(predose) and 2 h (end time)	3 mg/kg q.d.	PK tim h(、 h、 h、 h(tim h、 h、 h、 h、 an
2(14)	Test drug(8) Positive drug(4) Placebo(2)	4 mg/kg q.d.	The same as above	4 mg/kg b.i.d.	4 mg/kg b.i.d.	The same above	The same above	4 mg/kg q.d.	Th as
3(14)	Test drug(8) Positive drug(4) Placebo(2)	6 mg/kg q.d.	The same as above	6 mg/kg b.i.d.	6 mg/kg b.i.d.	The same above	The same above	6 mg/kg q.d.	PK tim h(、 h、 h、 h(tim h、 h、 h、 h、 h、 h、 h、 an

*Voriconazole was infused intravenously (i.v.) at a constant rate for a fixed time (2 hours ±3 min) by dosage design in each cohort. If the 3 mg/kg single dosage was well tolerated, after the three-day washout, the participant was administered the 3 mg/kg dosage every 12 h i.v. thereafter until the morning of day 8, as well as the 4 mg/kg and 6 mg/kg cohorts.

*In the cohort of 6 mg/kg, 72 h, 96 h and 120 h PK collection times were added in the design after day 8 administration.

*PK: Plasma pharmacokinetic sampling.

TABLE 2. Demographic characteristics

	3 mg/kg Test drug (n=8)	3 mg/kg Positive drug (n=4)	4 mg/kg Test drug (n=8)	4 mg/kg Positive drug (n=4)	6 mg/kg Test drug (n=8)	6 mg/kg Positive drug (n=4)	Placebo(n=6

Age(year)	**Age(year)**	**Age(year)**	**Age(year)**	**Age(year)**	**Age(year)**	**Age(year)**	**Age(year)**	**Age(year)**	**Age(year)**
Mean(SD)	27.25±5.5	33.5±4.12		35±3.66	29.75±7.41		31.5±7.27	29.5±2.38	27.17±4.12
Height(cm)	**Height(cm)**	**Height(cm)**	**Height(cm)**	**Height(cm)**	**Height(cm)**	**Height(cm)**	**Height(cm)**	**Height(cm)**	**Height(cm)**
Mean(SD)	159.88±6.35)	161.50±4.08		162.63±10.01	165.63±6.02		164.13±6.8	165.25±8.61	163.50±7.96
Weight(kg)	**Weight(kg)**	**Weight(kg)**	**Weight(kg)**	**Weight(kg)**	**Weight(kg)**	**Weight(kg)**	**Weight(kg)**	**Weight(kg)**	**Weight(kg)**
Mean(SD)	56.49±6.14)	56.43±4.32		60.85±7.31	59.55±8.26		60.08±6.47	62.63±6.78	57.78±5.79
BMI(kg/m^2)	**BMI(kg/m^2)**	**BMI(kg/m^2)**	**BMI(kg/m^2)**	**BMI(kg/m^2)**	**BMI(kg/m^2)**	**BMI(kg/m^2)**	**BMI(kg/m^2)**	**BMI(kg/m^2)**	**BMI(kg/m**
Mean(SD)	22.08±1.76)	21.60±0.81		22.96±0.65	21.63±1.84		22.31±2.06	22.92±2.12	21.58±1.11

TABLE3 Treatment Emergent Adverse events

			3 mg/kg Test drug (n=8)n/cases	3 mg/kg Positive drug (n=4) n/cases	4 mg/kg Test drug (n=8) n/cases	4 mg/kg Positive drug (n=4) n/cases	6 mg/kg Test drug (n=8) n/cases	6 mg/kg Positive drug (n=4) n/cases	Placebo(N= n/cases
Body system(SOC)	Adverse event(PT)	Adverse event(PT)	2/2	3/4	6/9	2/2	15/54	3/9	2/3
Ear and Labyrinth disorders			0/0	0/0	0/0	0/0	1/1	0/0	0/0
	Ear discomfort	Ear discomfort	0/0	0/0	0/0	0/0	1/1	0/0	0/0
Infection and infestations			0/0	0/0	0/0	0/0	1/1	0/0	0/0
	Herpesvirus infections	Herpesvirus infections	0/0	0/0	0/0	0/0	1/1	0/0	0/0
Investigations			2/2	3/4	3/5	2/2	5/8	1/1	1/1
	White blood cell decreased	White blood cell decreased	0/0	1/1	0/0	0/0	0/0	0/0	0/0
	*ALT increased	*ALT increased	0/0	1/1	2/2	0/0	2/2	0/0	0/0
	Urine leukocyte	Urine leukocyte	0/0	0/0	0/0	0/0	1/1	0/0	0/0
	Proteinuria	Proteinuria	0/0	0/0	0/0	1/1	0/0	0/0	0/0
	Eosinophil percentage increased	Eosinophil percentage increased	0/0	0/0	0/0	0/0	0/0	0/0	1/1
	*AST increased	*AST increased	0/0	2/2	3/3	0/0	2/2	0/0	0/0
	Electrocardiogram QT interval prolonged	Electrocardiogram QT interval prolonged	0/0	0/0	0/0	1/1	0/0	1/1	0/0

	Electrocardiogram abnormal	Electrocardiogram abnormal	1/1	0/0	0/0	0/0	0/0	0/0	0/0
	Hypokalemia	Hypokalemia	0/0	0/0	0/0	0/0	3/3	0/0	0/0
	Hypotension	Hypotension	1/1	0/0	0/0	0/0	0/0	0/0	0/0
Nevous System Disorders			0/0	0/0	1/1	0/0	3/5	1/1	1/1
	Headache	Headache	0/0	0/0	0/0	0/0	0/0	0/0	1/1
	Dizziness	Dizziness	0/0	0/0	1/1	0/0	1/1	1/1	0/0
	Vertigo	Vertigo	0/0	0/0	0/0	0/0	3/4	0/0	0/0
Psychiatric Disorders			0/0	0/0	1/1	0/0	7/7	0/0	0/0
	Hallucination	Hallucination	0/0	0/0	0/0	0/0	2/2	0/0	0/0
	Insomnia	Insomnia	0/0	0/0	1/1	0/0	5/5	0/0	0/0
Skin and Subcutaneous Tissue disorders			0/0	0/0	0/0	0/0	1/1	0/0	0/0
	Urticaria	Urticaria	0/0	0/0	0/0	0/0	1/1	0/0	0/0
Gastrointestinal Disorders			0/0	0/0	0/0	0/0	0/0	0/0	1/1
	Oral ulcer	Oral ulcer	0/0	0/0	0/0	0/0	0/0	0/0	1/1
Cardiac Disorders			0/0	0/0	0/0	0/0	2/4	0/0	0/0
	Infranodal extrasystole	Infranodal extrasystole	0/0	0/0	0/0	0/0	1/1	0/0	0/0
	First Degree A-V block	First Degree A-V block	0/0	0/0	0/0	0/0	1/3	0/0	0/0
Eye Disorders			0/0	0/0	1/2	0/0	9/27	2/7	0/0
	Xanthopia	Xanthopia	0/0	0/0	0/0	0/0	2/11	1/1	0/0
	Periorbital swelling	Periorbital swelling	0/0	0/0	0/0	0/0	1/1	0/0	0/0
	Chloropia	Chloropia	0/0	0/0	0/0	0/0	1/1	0/0	0/0
	Photopsia	Photopsia	0/0	0/0	1/1	0/0	2/3	1/4	0/0
	Blurred vision	Blurred vision	0/0	0/0	0/0	0/0	2/4	1/2	0/0
	Photophoby	Photophoby	0/0	0/0	1/1	0/0	2/7	0/0	0/0

TABLE4. PK parameters after single doses of 3 mg/kg, 4 mg/kg and 6 mg/kg administration

Parameter	Parameter	Parameter	$t_{1/2}$(h)	T_{max}(h)*	C_{max}(ng/mL)	$AUC_{0\text{-}48h^*}$(h*ng/mL)	$AUC_{0-\infty}$[?](h*ng/mL)	λ_z
Day1-3	Test drug 3 mg/kg(N=8)	Mean±SD	5.91±2.19	2(1.5,2)	1395±226.21(1	5882.48±2504.66	6607.86±2962.08	0.0834(0
						(3349.85~11501)		
		CV%	**37.07**	**9.12**	**16.22**	**42.58**	**46.96**	48.05

Test drug 4 mg/kg(N=8)	Mean±SD	7.38±4.37	2(1.5,2)	2001.25±314.48 [illegible]	[illegible]	[illegible]	[illegible]
	CV%	**59.30**	**9.12**	**15.71**	**63.84**	**67.39**	62.09
Test drug 6 mg/kg(N=8)	Mean±SD	7.74±1.14	2(1.5,2)	3461.25±558.99 [illegible]	[illegible]	[illegible]	[illegible]
	CV%	**14.79**	**12.34**	**16.15**	**22.06**	**20.65**	13.83
Positive drug 3 mg/kg(N=4)	Mean±SD	4.10±1.91	2(2,2)	1312.50±188.36 [illegible]	[illegible]	[illegible]	[illegible]
	CV%	**0**	**14.35**	**67.95**	**70.16**	**42.09**	61.34
Positive drug 4 mg/kg(N=4)	Mean±SD	9.48±6.05	2(1.5,2)	2162.50±400.53 [illegible]	[illegible]	[illegible]	[illegible]
	CV%	**63.81**	**13.33**	**18.52**	**52.08**	**55.07**	**77.55**
Positive drug 6 mg/kg(N=4)	Mean±SD	7.56±1.41	2(2,2)	3177.50±736.13 [illegible]	[illegible]	[illegible]	[illegible]
	CV%	**18.69**	**0.00**	**23.17**	**28.63**	**27.75**	18.39

TABLE 5 . PK parameters after multiple doses of 3 mg/kg, 4 mg/kg and 6 mg/kg administration

Pk parameter	Pk parameter	Pk parameter	unit	3 mg/kg Mean±SD	3 mg/kg CV%	4 mg/kg Mean±SD	4 mg/kg CV%	6 mg/kg Mean±SD	6 mg/kg CV%
Test drug (3 mg/kgN=7,others N=8)	day8-10(6 mg/kg: days 8-13)	$t_{1/2}$	h	11.79±5.77	**48.94**	21.4±21.88	**102.23**	9.45±0.95	**10**[illegible]
		*$T_{max,ss}$	h	170(170,170)	**0.00**	170(169.5,170)	**0.1**	170(169.5,170)	**0.**[illegible]
		$C_{max,ss}$	ng/mL	3550±891.87 (2660~4820)	**25.12**	5337.50±1626 [illegible] (3400~8520)	**30.47**	9617.5±1545.[illegible]	[illegible]
		$C_{min,ss}$	ng/mL	**1486.29±783.[illegible]**	**52.71**	**2616.13±16[illegible]**	**62.48**	**5378.75±119[illegible]**	[illegible]
		$C_{av, ss}$	ng/mL	**2245.32±847.[illegible]**	**37.76**	**3631.05±165[illegible]**	**45.64**	**7075.52±128[illegible]**	[illegible]
		#$AUC_{0\text{-}12h,\ ss}$	h*ng/mL	26943.86±101[illegible] (16418.25~42487.50)	**37.76**	59226.25±211[illegible] (28237.5~72677.5)	**45.64**	84906.25±153[illegible]	[illegible]
		#$AUC_{0\text{-}[?]}$	h*ng/mL	63950.38±451[illegible] (26268.95~133381.13)	**70.54**	178049.94±22[illegible]	**125.3**[illegible]	[illegible] (142321.17~3359[illegible]	[illegible]
		$AUC_{\_\%Extrap\_obs}$	%	**7.46±7.07**	**94.81**	**15.62±22.65**	**144.98**	**0.31±0.13**	**43**[illegible]
		Vz, ss/F	L	**111.55±23.92**	**21.5**	**156.01±79.35**	**50.85**	**132.44±24.36**	[illegible]
		Cl_{ss}/F	L/h	**6.93±1.93**	**27.84**	**6.60±2.81**	**42.57**	**4.35±0.58**	**13**[illegible]
		R_{AUC}	/	5.18±1.07	**20.58**	5.59±1.15	**20.63**	5.82±0.47	**8.**[illegible]
		R_{Cmax}	/	2.50±0.44	**17.46**	2.63±0.46	**17.47**	2.79±0.28	**10**[illegible]
Positive drug\(N=4 in each dose)	Day 8-10(6 mg/kg:day 8-13)	$t_{1/2}$	h	15.27±16.22	**106.21**	29.55±18.04	**61.05**	9.84±2.72	**27**[illegible]
		*$T_{max,ss}$	h	170(170,170)	0	170(169.5,170)	**0.15**	170(170,170)	0
		$C_{max,ss}$	ng/mL	8090.00±2101[illegible] (5710.00~10200.00)	**32.88**	6807.5±1920.[illegible] (3930~7870)	**28.21**	8090.00±2101[illegible] (5710~10200)	**25**[illegible]
		$C_{min,ss}$	ng/mL	**1498.25±100[illegible]**	**67.26**	**3847.50±168[illegible]**	**43.83**	**4020.00±191[illegible]**	**47**[illegible]

$C_{av,\ ss}$	ng/mL	**2302.66±1054.58**	**45.80**	**4935.52±1758.53**	**35.63**	**5552.81±1944.11**	**34**
#$AUC_{0\text{-}12h,\ ss}$	h*ng/mL	66633.75±23245.88	**34.88**	59226.25±21135.63	**35.68**	66633.75±23245.88	**34**
		(39932.50~91655)		(28237.5~72677.5)		(39932.50~91655)	
#$AUC_{0\text{-}[?]}$	h*ng/mL	166054.79±93113.45	**56.08**	268193.50±168209.02	**62.72**	166054.79±93113.45	**56**
		(72573.27~273153.39)		(48854.73~450873.83)		(72573.27~273153.39)	
$AUC_{\_\%Extrap\_obs}$	%	**10.98±20.35**	**185.36**	**28.76±20.94**	**72.81**	**1.40±0.91**	**64**
Vz, ss/F	L	**118.94±44.63**	**37.51**	**159.80±50.18**	**31.39**	**116.28±13.62**	**11**
Cl_{ss}/F	L/h	**7.21±3.07**	**42.59**	**4.56±1.82**	**39.92**	**6.41±2.85**	**44**
R_{AUC}	/	5.26±0.99	**18.83**	5.26±0.99	**18.83**	5.52±0.76	**13**
R_{Cmax}	/	2.68±0.72	**26.98**	3.11±0.57	**18.35**	2.55±0.34	**13**

*T_{max} **medium** (min,max),#: Mean±SD(min,max),one subject withdraw due to adverse reaction before