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Pharmacokinetics of Amphotericin B Liposome for Infusion in Healthy Subjects Based on a Bioequivalence Study

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A B S T R A C T

Purpose: The aim of this study was to evaluate the pharmacokinetic characteristics and safety of Amphotericin B liposome for infusion in healthy volunteers based on a pilot bioequivalence clinical trial between a generic formulation and Ambisome®.

Methods: This single centre, randomized, single-dose, open-label, 2-way crossover bioequivalence study was conducted in healthy volunteers at the dose of 3 mg/kg. Blood samples were collected at pre-defined time points up to 1106 h after the start of the 2-h infusion. Plasma concentrations of free amphotericin B (liposome-unbound) and liposome-encapsulated amphotericin B were determined. Pharmacokinetic parameters were calculated using non-compartmental model. The formulations were considered bioequivalent if the 90% confidence intervals (CIs) of the geometric mean ratio of Cmax and AUCs of both products for free amphotericin B (liposome-unbound) and liposome-encapsulated amphotericin B were within 80.00%-125.00% for Ln-transformed data.

Results and conclusion: Of the dosed 60 subjects, 56 subjects had completed the study. The generic liposomal amphotericin B for injection is bioequivalent to Ambisome® in terms of the Pharmacokinetic parameters for free amphotericin B (liposome-unbound) and liposome-encapsulated amphotericin B

Keywords: Amphotericin B liposome for infusion; Pharmacokinetics; Bioequivalence; Healthy subjects

Introduction

Amphotericin B is amacrocyclic, polyene, antifungal antibiotic that is widely used since 1950s for the treatment of systemic fungal infections caused mostly by Candida and Aspergillus [1, 2]. Amphotericin B, the polyene class of antifungal agents, is still an important option for the prevention and treatment of invasive fungal diseases due to its broad spectrum and well-documented clinical efficacy. Amphotericin B acts by irreversibly binding its target, the ergosterol components of the fungal cell membrane, leading to cell permeability alterations and therefore resulting in the leakage of the cell contents and eventual cell death. Due to lack of selectivity for fungal versus human cells, the clinical application of Amphotericin B was limited by side effects, such as nephrotoxicity and infusion-related reactions [3]. Three lipid formulations, namely liposomal amphotericin B, amphotericin B lipid complex and amphotericin B colloidal dispersion (ABCD), were approved in the 1990s to overcome these problems [4]. Among the four amphotericin B formulations in market, Ambisome® is widely used in clinical based on its better safety profiles compared with other amphotericin B formulations. Ambisome® has established detailed clinical PK/efficacy/safety profiles since its first approved in 1990. Ambisome®, the liposomal formulation of amphotericin B was developed and manufactured by Gilead Sciences, Inc. The liposomal bilayer membrane contains hydrogenated soy phosphatidylcholine, cholesterol, distearoyl phosphatidyl glycerol and Amphotericin B in a molecular ratio of 2:1:0.8:0.4. The kidney distribution of amphotericin B is significantly reduced after receiving Ambisome® and the occurrence of nephrotoxicity is therefore lowered, but the potent antifungal activity remains the same as conventional amphotericin B [5].

Circulating liposomes like liposomal amphotericin B can release drug so that free drug (unbound and protein-bound) and liposomal drug pools may exist simultaneously within the body after administration. These drug pools differ in their pharmacokinetic, safety, and efficacy profiles. Especially for free amphotericin B, the active drug, reflects the rate and extent of drug release from the liposomal particles. Therefore, it is necessary to develop reliable methods to determine these different types of amphotericin B in plasma to fully characterize the Biopharmaceutical characteristics of liposomal drugs [6].

Amphotericin B liposome for infusion used in our study is the generic product of Ambisome® (the reference formulation) developed by Sun Pharmaceutical Medicare Ltd., India. In the preclinical study the same structure and Pharmacokinetic (PK) profiles of Amphotericin B liposome for infusion were thoroughly proven as the same as Ambisome®. This study was designed to examine the pharmacokinetics of Amphotericin B liposome

for infusion in healthy subjects, and simultaneously to evaluate the bioequivalence of the two preparations. Free amphotericin B, and liposomal amphotericin B) in plasma were determined to fully clarify the PK behaviours of Amphotericin B liposome for infusion.

Materials and Methods

Study design and Subjects

Study protocol was approved by Advarra Institutional Review Board, Ontario, Canada. The clinical phase of the study was conducted at Syneos Health Clinique inc., 2500, rue Einstein, Quebec, Canada in accordance with the principles of the Declaration of Helsinki, U.S. applicable Code of Federal Regulations (title 21) and the guidance for Good Clinical Practice (GCP). Written informed consent was given by all participants prior to initiation of study procedures. This was a single centre, randomized, single-dose, open-label, 2-way crossover bioequivalence study in healthy human males and females. The primary objective was to compare the rate and extent of absorption of amphotericin B liposome for injection determine bioequivalence, based on area under the curve (AUC) from time 0 to the last measurable concentration (AUC_{0-t}), AUC from time 0 extrapolated to infinity ($AUC_{0-\infty}$) and C_{max} of free amphotericin B (liposome-unbound) and liposome-encapsulated amphotericin B.

Sample size

Based on anticipated coefficient of variation of approximately 17% for AUC of liposome-encapsulated amphotericin B and an expected ratio of AUC within 0.87 and 1.13, the study should have a power of at least 80% to show bioequivalence with 50 subjects. In order to account for possible dropouts, 60 subjects were included in the study.

Treatments and administration

Eligible participants were dosed after a supervised overnight fast of at least 10 hours. Subjects were administered the test (A, Batch number: HKR0712, Sun Pharmaceutical Medicare Ltd., India) or reference (B, Lot number: 009043, Gilead Science, Inc., USA) medication as per the randomization scheme as a 3 mg/kg dose by I.V. infusion over a period of 120 minutes using a volume-controlled infusion device. The washout period of at least 70 days was chosen to allow the complete elimination of the drug before subsequent drug administration and to avoid important carry-over effect expected for the non-encapsulated drug fraction. In order to reduce the likelihood of occurrence of infusion-related reactions, for safety reasons, 1000 mg of acetaminophen and 50 mg of diphenhydramine were administered orally 30 minutes before the start of the infusion. Considering availability of infusion pump, subjects were dosed in the group of 12 subjects. Hence, subjects were administered the study drug in total five equal groups.

In each period, blood samples were collected in K_2EDTA tubes within one hour prior to start of study drug infusion (0 hour) and 0.500, 1.00 1.50, 2.00 (immediately prior to the end of infusion), 2.083, 2.167, 2.25, 2.333, 2.5, 2.75, 3.00, 3.50, 4.00, 6.00, 8.00, 14.0, 26.0 (Day 2), 50.0 (Day 3), 98.0 (Day 5), 122 (Day 6) hours after start of study drug infusion for free amphotericin B (liposome-unbound) and liposome-encapsulated amphotericin B. In addition, for free amphotericin B (liposome-unbound) only, blood samples were collected 362 (Day 16), 602 (Day 26), 842 (Day 36), and 1106 (Day 47) hours after start of study drug infusion. A dead-volume I.V. catheter was used for blood collection to avoid multiple skin punctures. Blood sampling was performed in the opposite arm than the one used for study drug infusion for the first 26 hours post-dose. Subjects were return back to the facility for all the subsequent blood draws post 26 hour time point. Since amphotericin B is light sensitive, UV filters were used on ambient light and samples were protected from direct natural light. Blood samples were cooled in an ice/water bath and were centrifuged at 2000 ±5 g for at least 10 minutes at approximately 4°C. Two aliquots of at least 0.350 mL of plasma (for liposome-encapsulated amphotericin B) and two aliquots of at least 0.360 mL of plasma (for free amphotericin B (liposome-unbound)) were dispensed into amber polypropylene tubes, containing a 20% dextrose 25% glycerol solution, resulting in a plasma:buffer ratio of 40% v/v. The aliquots were subsequently transferred to a -80°C freezer until transferred to analytical facility.

Analytical Methods

The validated bioanalytical methods were developed for the quantification of free amphotericin B (liposome-unbound) and liposome-encapsulated amphotericin B in plasma. Bioanalytical method validation was done as per USFDA bioanalytical method validation guidance with evaluation for specificity, sensitivity, precision and accuracy, stability, recovery and dilution integrity. In accordance with study protocol these methods were employed on samples from subjects who had completed both the periods of the study including the subjects who were dropped from the study due to adverse events.

Safety evaluation

Safety assessments included adverse events (AEs; overall, by severity, and by relation to study treatment which based on clinical observations and laboratory tests). Treatment Emergent Adverse Events (TEAEs) were collected during and after dosing, including all subjective symptoms and objective signs. Vital signs measurements (BP, HR, RR, and oral temperature) were performed at the time of screening procedures and study exit procedures. In addition, BP and HR were taken prior to study drug infusion and 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hours (± 10 minutes) after start of the study drug infusion in each period. Oral temperature was prior to study drug infusion and four and 12 hours (± 15 minutes) after start of study drug infusion in each period. ECG measurements were performed at the time of screening, prior to start of drug infusion and 0.25, 0.5, 1.00, 2.00, and 3.00 hours (± 10 minutes) after start of study drug infusion in each period and at the time of and study exit procedures.

Pharmacokinetic and Statistical Analysis

Pharmacokinetic parameters were calculated using Phoenix® Win-Nonlin® (Version 6.4) using non-compartmental analyses. Statistical analyses were performed on individual pharmacokinetic parameters obtained for free amphotericin B (liposome-unbound) and liposome-encapsulated amphotericin B, using the SAS® package (SAS® Institute Inc., USA, Version 9.4). The Mixed model ANOVA was used to analyze Ln-transformed pharmacokinetic parameters (AUC_{0-t}, AUC_{0-inf} and $C_{max)}$ that contain terms for Group, Sequence, Group*Sequence, Period (Group), Treatment and Group*Treatment as fixed effects and Subject (Group*Sequence) as random effect. The consistency was tested for test reference relationship across the Groups at 10% level of significance. The Sequence effect were to be tested at the 0.10 level of significance and all other main effects (i.e. Group, Group*Sequence, Treatment &Period (Group)) were to be tested at the 0.05 level of significance against the p-values in Type-III test of fixed effects from ANOVA. Based on pair wise comparisons of the Ln-transformed $AUC_{0-t,}$ AUC_{0-inf} and C_{max} data, the ratios of the least-square means, calculated according to the formula "($e^{(LSM\ Treatment\ (A)\ -\ LSM\ Treatment\ (B))}$ X 100) %", as well as the 90% geometric confidence intervals for AUC_{0-t}, AUC_{0-inf} and C_{max} were determined.

Results

Demographic Characteristics

In this study, 121 subjects were screened, of these, 71 subjects were enrolled (subjects who participated in Period 1 check-in procedures). Sixty (60) subjects (28 females and 32 males) were randomized and dosed in this study; of these, 56 subjects completed both the study periods. The mean age, height, weight and BMI of all the subjects who included in safety population and completed the study are presented in (Table 1).

Table 1 Demographic profile and baseline clinical characteristics of subjects

Characteristic	**Safety population N=60**	**Per Protocol population N=56**
Sex, No. (%)	**Men:** 32(53.3%) **Women:** 28(46.7%)	**Men:** 29 (51.79%) **Women:** 27 (48.21%)
Age, years (mean ± SD)	45.9 ± 13.29	46.4±13.08
Height, cm (mean ± SD)	168.51 ± 9.23	168.38±9.52
Weight, kg (mean ± SD)	71.40 ± 10.97	71.39±11.06
Body mass index, kg/m^2 (mean ± SD)	25.064 ± 2.63	25.096±2.63

Plasma Pharmacokinetics

Out of the dosed sixty (60) subjects, fifty-six (56) subjects completed both the periods of the study. In accordance with the study protocol, plasma samples from all subjects who had completed both the periods of the study including subject who was dropped from the study due to adverse event was assayed for free amphotericin B (liposome-unbound) and liposome-encapsulated amphotericin B.

Data of two subjects were not analysed due to exceeding the total pump interruption time than allowed time limit and due to two consecutive missing sample at C_{max} point. Data of 54 subjects were used for Pharmacokinetic and statistical analysis of free amphotericin B (liposome-unbound) and liposome-encapsulated amphotericin B.

The mean and Ln-transformed plasma concentration-time profiles after single dose administration of two different liposomal amphotericin B formulations are presented in Fig.1

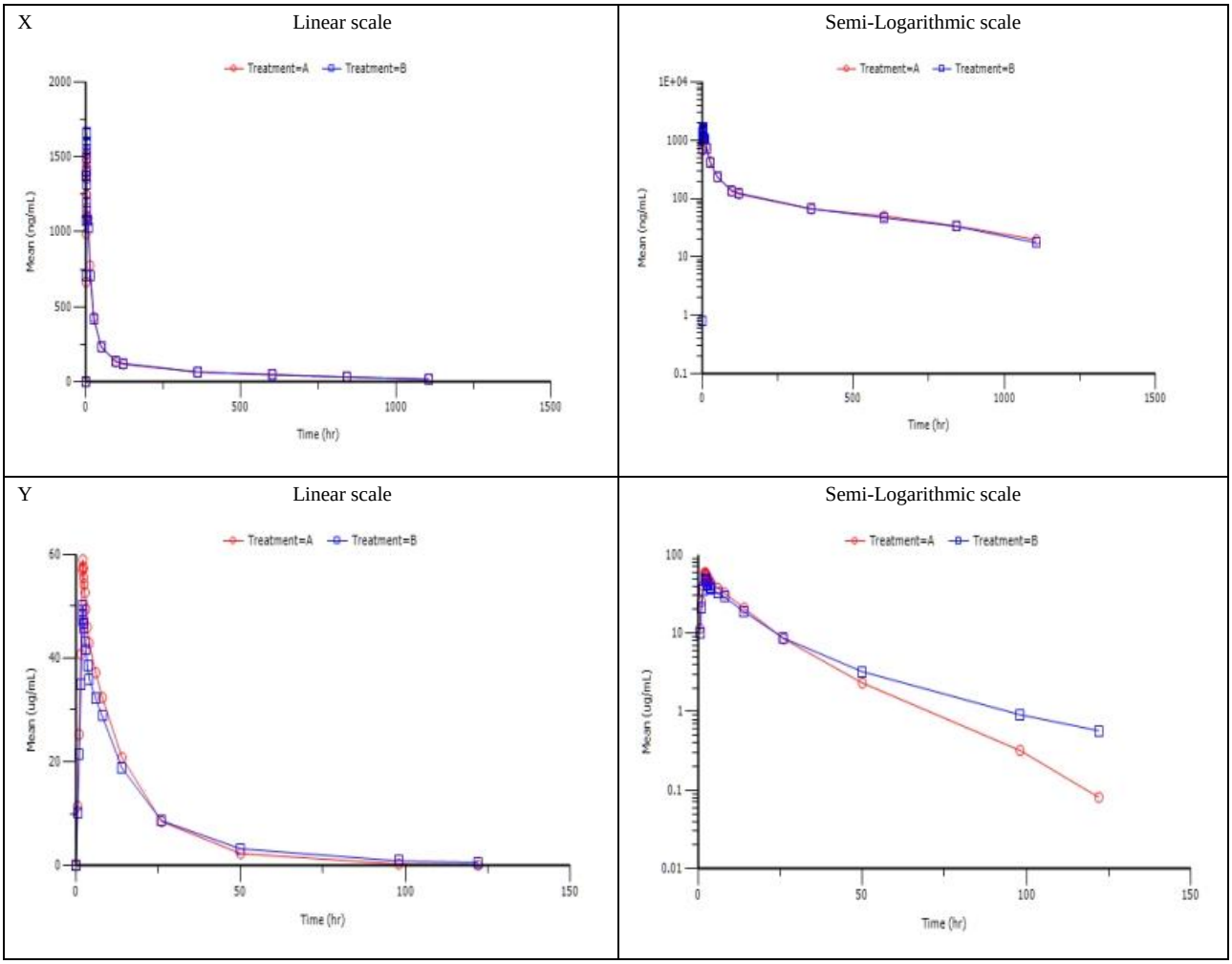

Fig.1 Mean plasma concentration-time curves of Free amphotericin B (Liposome-unbound) (X)and Liposome-encapsulated amphotericin B (Y) amphotericin B after IV infusion of the test and refer drug in healthy subjects

The mean, standard deviation, standard deviation, geometric mean, coefficient of variation, minimum, median, maximum and range were calculated for AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, $t_{1/2}$ and % AUC extrapolation of free amphotericin B (liposome-unbound) and liposome-encapsulated amphotericin B.

Resulting pharmacokinetic parameters of free amphotericin B (liposome-unbound) are summarised in Table 2.

Table 2 The main pharmacokinetic parameters of free amphotericin B after IV infusion of the test or reference drugs.

Free amphotericin B PK Parameters (Units)	**Mean ± SD (CV%) (N=54)**	
	Test Drug (A)	**Reference Drug (B)**
AUC_{0-t} (ng.h/mL)	93262.42 ± 28285.25 (30.33%)	92774.95 ± 26394.62 (28.45%)
AUC_{0-inf} (ng.h/mL)	113726.79 ± 39088.26 (34.37%)	115981.18 ± 40925.90 (35.29%)
C_{max}(ng/mL)	1609.45 ± 243.59 (15.13%)	1729.25 ± 261.34 (15.11%)
***T_{max} (h)**	2.073 (1.986 - 2.999)	2.072 (1.988 - 2.493)
K_{el} (h^{-1})	0.00168 ± 0.00056 (33.24%)	0.00163 ± 0.00071 (43.32%)
$t_{1/2}$ (h)	458.27 ± 154.30 (33.67%)	501.03 ± 221.45 (44.20%)
% AUC Extrapolation	17.143 ± 5.972 (34.84%)	18.490 ± 7.856 (42.49%)

*Expressed in terms of median (range)

Resulting pharmacokinetic parameters of Liposome-encapsulated amphotericin B are summarised in Table 3.

Table 3 The main pharmacokinetic parameters of Liposome-encapsulated amphotericin B after IV infusion of the test or reference drugs

Encapsulated amphotericin B	**Mean ± SD (CV%) (N=54)**	
PK Parameters (Units)	**Test Drug (A)**	**Reference Drug (B)**
AUC_{0-t} (µg.h/mL)	826.12 ± 406.29 (49.18%)	823.92 ± 334.03 (40.54%)
AUC_{0-inf} (µg.h/mL)	835.21 ± 408.37 (48.89%)	848.03 ± 339.97 (40.09%)
C_{max}(µg/mL)	61.4648 ± 15.68 (25.52%)	52.2478 ± 13.88 (26.57%)
***T_{max} (h)**	2.084 (1.986 - 2.488)	2.080 (1.988 - 2.993)
K_{el} (h^{-1})	0.06044 ± 0.01780 (29.44%)	0.02499 ± 0.00533 (21.34%)
$t_{1/2}$ (h)	12.50 ± 3.80 (30.37%)	28.88 ± 5.66 (19.60%)
% AUC Extrapolation	1.30 ± 0.83 (63.78%)	3.08 ± 1.38 (44.74%)

*Expressed in terms of median (range)

The last point for plasma collection was 1106 h after the start of the 2-h infusion, therefore the elimination phase of the liposomal drug was fully depicted.

Bioequivalence Evaluation

Healthy subjects received a single oral of the test and reference Amphotericin B liposome for infusion. The primary evaluation endpoints of the study were geometric least squares mean ratio of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values for free and encapsulated amphotericin B after administration of test and reference treatment, which were evaluated for bioequivalence (Table 4).

Table 4 Geometric least squares mean ratios and 90% CIs for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$following administration of IV infusion of 3 mg/kg of test or reference drugs in healthy subjects

Free amphotericin B (liposome-unbound) (N = 54)					
PK Parameters (Unit)	**Least Squares Geometric Means**		**% T/R Ratio**	**90% C.I.**	**Intra-Subject CV %**
	Test	**Reference**			
AUC_{0-t} (ng.h/mL)	89579.06	89494.23	100.09	97.49 to 102.77	8.17
$AUC_{0-\infty}$ (ng.h/mL)	108297.29	110346.71	98.14	95.15 to 101.23	9.59
C_{max}(ng /mL)	1587.50	1708.54	92.92	91.04 to 94.83	6.29
Liposome-encapsulated amphotericin B (N = 54)					
AUC_{0-t} (µg.h/mL)	729.18	756.95	96.33	91.99 to 100.88	14.31
$AUC_{0-\infty}$ (µg.h/mL)	738.75	781.07	94.58	90.39 to 98.97	14.08
C_{max}(µg /mL)	59.19	50.13	118.07	113.52 to 122.81	12.19

Free amphotericin B (liposome-unbound): The ratios of the least-squares geometric means (and 90% geometric confidence intervals) of the Test to Reference product (A/B) were 100.09 (97.49 to 102.77) % for AUC_{0-t}, 98.14 (95.15 to 101.23) % for AUC_{0-inf} and 92.92 (91.04 to 94.83) % for C_{max}. The intra-subject CVs for AUC_{0-t}, AUC_{0-inf} and C_{max} were 8.17%, 9.59% and 6.29% respectively.

Liposome-encapsulated amphotericin B: The ratios of the least-squares geometric means (and 90% geometric confidence intervals) of the Test to Reference product (A/B) were 96.33 (91.99 to 100.88) % for AUC_{0-t}, 94.58 (90.39 to 98.97) % for AUC_{0-inf} and 118.07 (113.52 to 122.81) % for C_{max}. The intra-subject CVs for AUC_{0-t}, AUC_{0-inf} and C_{max} were 14.31%, 14.08% and 12.19% respectively.

From the above results of free amphotericin B (liposome-unbound) and liposome-encapsulated amphotericin B, it can be concluded that the AUC_{0-t}, AUC_{0-inf} and C_{max} results were within the acceptable limits of 80.00% to 125.00% for concluding bioequivalence.

Safety

All (60) subjects received at least one dose of the study medication and comprised the safety population. The results from the subjects who completed study exit procedures, including laboratory tests, ECGs, vital signs measurements, and urine pregnancy test confirmed the absence of significant changes in the subjects' state of health.

A total of 220 TEAEs were reported by 49 of the 60 subjects who received at least one dose of the study medication (safety population). 106 TEAEs reported by 69.0% (n=40) of the 58 subjects who received test treatment and 114 TEAEs reported by 69.0% (n=40) of the 58 subjects who received reference treatment.

The most commonly reported TEAEs were "Somnolence", "Back pain", "Hot flush", "Muscle spasm", and "Nausea" of subjects who constituted the safety population, respectively. As per prescribing information, "Somnolence", "Back pain", "Hot flush", "Muscle spasm", and "Nausea" are commonly reported with the use of amphotericin B.

No deaths and serious AEs were reported during this study. The total number of TEAEs following administration of each treatment and the total number of subjects who reported TEAEs was similar between both treatment groups. Although there was a high number of TEAEs, the majority of the AEs were mild in severity and transient, had a probable relation to the study drug, and resolved spontaneously without medical intervention. There were no relevant differences between each treatment group when comparing the number of subjects for each MedDRA® PT.

Table-5: System wise Treatment Emergent Adverse Events experienced by the subjects from the test and reference treatment arm

System Organ Class	Treatment Group	
	A	**B**
Number of subjects dosed	58	58
Cardiac disorders	1 (1.7%)	2 (3.4%)
Ear and labyrinth disorders	1 (1.7%)	0
Gastrointestinal disorders	9 (15.5%)	11 (19.0%)
General disorders and administration site conditions	9 (15.5%)	8 (13.8%)
Immune system disorders	0	1 (1.7%)
Infections and infestations	4 (6.9%)	4 (6.9%)
Injury, poisoning and procedural complications	2 (3.4%)	5 (8.6%)
Investigations	1 (1.7%)	0
Musculoskeletal and connective tissue disorders	21 (36.2%)	25 (43.1%)
Nervous system disorders	24 (41.4%)	24 (41.4%)
Respiratory, thoracic and mediastinal disorders	7 (12.1%)	4 (6.9%)
Skin and subcutaneous tissue disorders	1 (1.7%)	0
Vascular disorders	13 (22.4%)	12 (20.7%)

Discussion

Liposomes have been considered promising and versatile drug vesicles. Compared with traditional drug delivery systems, liposomes exhibit better properties, including site-targeting, sustained or controlled release, protection of drugs from degradation and clearance, superior therapeutic effects, and lower toxic side effects. The PK of liposome formulation is jointly determined by the PK of carrier and drug release rate. After administered, there are many types of analytes in plasma, including encapsulated drugs and free drugs. Generally speaking, only free drugs are biologically active. For Amphotericin B liposome for infusion, the same plasma total pharmacokinetics does not mean the same tissue distribution, nor does it mean the same safety and efficacy. So, the BE establishment for Amphotericin B liposome for infusion does not only rely on a single analyte alone, but on multiple analytes [10].

Since the amount of free amphotericin B (liposome-unbound) is very small, the total amount of amphotericin B is close to the amount of liposome-encapsulated amphotericin B. Therefore, current regulatory agencies, including FDA and EMA, suggest detection of free amphotericin B (liposome-

unbound) and liposome-encapsulated amphotericin B. In addition, these regulatory principles recommend that the main PK parameters (C_{max} and AUCs) of all analytes should meet the BE criteria. According to the above guidance of regulatory agencies, our results showed that the Amphotericin B liposome for infusion manufactured by Sun Pharmaceutical Medicare Ltd., India, has established bioequivalence with Ambisome®.

The statistical analysis was performed using Mixed model ANOVA to analyze Ln-transformed pharmacokinetic parameters (AUC_{0-t}, AUC_{0-inf} and C_{max}) using non-compartmental analyses that contain terms for Group, Sequence, Group*Sequence, Period (Group), Treatment and Group*Treatment as fixed effects and Subject (Group*Sequence) as random effect. No statistically significant ($p>0.10$) Group*Treatment interaction was found for Ln-transformed pharmacokinetic parameters of Free amphotericin B (liposome-unbound) and Liposome-encapsulated amphotericin B,hence, the Group*Treatment term was dropped from the statistical model.

All other ANOVA effects were statistically insignificant (i.e. $p>0.05$ and $p>0.10$) for Free amphotericin B (liposome-unbound) and Liposome-encapsulated amphotericin B. The statistically significant effects can be ignored considering the analysis approach adopted for two way, cross over study design.

Bioequivalence was consistently established based on free amphotericin B (liposome-unbound) and liposome-encapsulated amphotericin B. All CIs for comparisons of C_{max} and AUCs ratios were within the 80.00-125.00% confidence Interval. In addition to PK bioequivalence, the test and reference products were well tolerated, and there were no significant differences between the safety profiles of the test and reference products. Those results showed the test product manufactured by Sun Pharmaceutical Medicare Ltd., India might be an alternative for Ambisome® for the treatment of invasive fungal infection.

Conclusion

The generic Amphotericin B liposome for infusion, manufactured by Sun Pharmaceutical Medicare Ltd., India is bioequivalent to Ambisome® in terms of the PK parameters for free amphotericin B (liposome-unbound) and liposome-encapsulated amphotericin B and with similar safety profiles as Ambisome®. Both the test and the reference products were well-tolerated, and the safety profile was similar.

Authors' contributions

Chirayu Shah contributed to manuscript writing and data analysis. Amaresh Chakra contributed to the study design, conception and data analysis. Pradeep Shahi contributed to study sample analysis. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of interest

Chirayu Shah, Amaresh Chakra and Pradeep Shahi are employees of Sun Pharmaceutical Industries Limited, India who is sponsor of the study and provided the funding for the study.

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