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ORIGINAL RESEARCH

A Phase 1, randomized, open-label crossover study to evaluate the safety and pharmacokinetics of 400 mg albaconazole administered to healthy participants as a tablet formulation versus a capsule formulation

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Background: Albaconazole is a novel triazole being developed for the oral treatment of fungal diseases. Once-weekly oral dosing with 400 mg albaconazole for 24 or 36 weeks resulted in high rates of clinical and mycological resolution for distal subungual onychomycosis, as well as a favorable safety and tolerability profile.

Purpose: To compare four 100-mg albaconazole capsules to one 400-mg albaconazole tablet for bioavailability, bioequivalence, tolerability, and safety.

Patients and methods: Forty participants were enrolled in this Phase I, open-label, two-sequence crossover study. Twenty participants were exposed to a single 400-mg tablet dose of albaconazole before being crossed over to a single dose of four 100-mg albaconazole capsules. The second group of 20 participants received the study products in reverse order. Blood samples were taken over 15 days post-dose to assess the plasma concentrations and pharmacokinetic parameters of albaconazole and its primary metabolite, 6-hydroxyalbaconazole. Safety was assessed throughout the study.

Results: The area under the curve (AUC) and maximum measured plasma concentration (C_{max}) of the albaconazole tablet were approximately 10% and 22% lower, respectively, than for the albaconazole capsules. Statistical significance was reached for the C_{max} but not for the AUC measurements ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$). Because the 90% confidence intervals based on the differences between the tablet and capsule were outside the 80%–125% range for both the C_{max} and AUC, we concluded that the formulations were not bioequivalent with respect to the rate or extent of absorption. Both formulations were safe and well-tolerated in this study. All adverse events (AEs) were generally mild and were mainly gastrointestinal- or nervous system-related (eg, dizziness, headache). No electrocardiogram findings were reported as an AE, and no serious AEs or deaths were reported.

Conclusion: The AUC and C_{max} of albaconazole after a single 400-mg oral dose administered as a tablet formulation were lower than those of a capsule formulation. Albaconazole tablets and capsules cannot, therefore, be considered bioequivalent.

Keywords: albaconazole, triazole, pharmacokinetics, onychomycosis

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Introduction

Albaconazole, previously known as UR-9825, is an antifungal agent with broad-spectrum activity that is being developed by Palau Pharma SA (Barcelona, Spain) for the treatment of fungal infections such as onychomycosis.[1,2] Albaconazole prevents

the conversion of lanosterol to ergosterol by inhibiting fungal 14α-demethylase, thus disrupting the formation of the fungal cell membrane.[3] Albaconazole has demonstrated in vitro activity against a broad spectrum of filamentous fungi and dermatophytes, as well as yeasts.[4–6] Its long half-life in humans (mean $t_{1/2}$ = 70.5 hours after single 240-mg doses) and good distribution to tissues may allow for weekly dosing (Stiefel, unpublished data).

A clinical study of distal subungual toenail onychomycosis demonstrated that once-weekly 400-mg oral doses of albaconazole for 24 or 36 weeks resulted in high rates of clinical and mycological resolution (Stiefel, unpublished data). Albaconazole was found to be safe and well-tolerated in all clinical studies performed to date with single oral doses from 5–800 mg, multiple daily doses of up to 1200 mg per day for 5 days, and once-weekly doses of up to 400 mg for up to 36 weeks (Stiefel, unpublished data). Weekly dosing of albaconazole is expected to offer advantages over treatment with the currently available systemic antifungal agents terbinafine and itraconazole, which require daily dosing and are linked to safety concerns, particularly hepatic toxicity (both agents) and cardiac dysfunction (itraconazole).[7–12]

Adverse events (AEs) associated with albaconazole treatment in previous studies have been generally mild or moderate in severity and transient in duration. Neither therapeutic nor supratherapeutic dosing regimens have been associated with clinically significant changes in vital signs or electrocardiogram (ECG) readings. No clinically relevant trends in increased liver enzyme counts were observed to be related to albaconazole treatment (Stiefel, unpublished data).

Albaconazole taken once weekly in 400-mg doses is expected to be a safe and effective dose regimen for the treatment of onychomycosis (Stiefel, unpublished data). The current Phase I study was conducted to compare a single 400-mg tablet of albaconazole with four 100-mg capsules for bioavailability, safety, tolerability, and bioequivalence.

Material and methods

Study participants

Inclusion criteria

Participants were males and females aged 18–45 years with a body mass index between 18.5 and 30 kg/m^2. For inclusion, participants must have (1) had baseline and laboratory screening parameters within normal ranges or be considered not clinically significant by the principal investigator and sponsor; (2) had alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin values lower than 1.5 times the upper limit of the normal range at screening; (3) been free of clinically significant diseases as determined by history, physical examination, and laboratory testing; (4) had negative results at screening for hepatitis B surface antigens, hepatitis B core antibodies, the anti-hepatitis C virus, human immunodeficiency virus antibodies, and urine drug screen; (5) been a nonsmoker or ex-smoker (nicotine must not have been used in the past 6 months); and (6) agreed to use a medically acceptable form of contraception throughout the study until 30 days after the final dose of the study product.

Exclusion criteria

Participants were excluded who (1) were pregnant, trying to become pregnant, or breastfeeding; (2) experienced clinically significant illness within 30 days of the screening examination; (3) received any investigational drug within 30 days of study day 1 or were scheduled to receive any investigational drug during the course of the study; (4) participated in a previous study of the same product; (5) had a history of any condition that could possibly affect the absorption of the drug, such as peptic ulcer disease, gastrectomy, or intestinal malabsorption; (6) had a history of anemia, iron deficiency, or iron depletion; (7) were immunocompromised or had a history of drug allergies; (8) presented with an ECG abnormality or ECG findings deemed clinically relevant; (9) had a QT interval corrected for heart rate (Fridericia's correction formula, QTcF) >450 ms; (10) had a clinically relevant history or presence of respiratory, gastrointestinal, renal, hepatic, hematologic, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, genitourinary, immunologic, dermatologic, or connective tissue disease or disorders; (11) had a known intolerance to the product's ingredients; or (12) had donated blood or had significant (≥250 mL) blood loss within 30 days of dosing or had donated plasma within 7 days of dosing.

Study medication

Albaconazole tablets (400 mg) contained albaconazole in combination with amino methacrylate copolymer, basic butylated methacrylate copolymer, aminoalkyl methacrylate copolymer E, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, iron oxide red, and purified water. Albaconazole capsules (100 mg) contained albaconazole in combination with amino methacrylate copolymer as film-coated microcrystalline cellulose pellets, talc, colloidal SiO_2, hydrochloric acid, anhydrous alcohol, and purified water.

Study design

This Phase I, single-center, randomized, open-label, two-period, two-sequence crossover study was designed to compare the pharmacokinetics of a single 400-mg albaconazole tablet with those of four 100-mg albaconazole capsules. The study consisted of four phases: (1) screening (day −29 to day −2), (2) the first dose period with pharmacokinetic (PK) blood sampling (day −1 to day 16), (3) a washout period (at least 12 days), and (4) a second dose period with PK blood sampling (day −1 to day 16). Twenty participants took four 100-mg albaconazole capsules before crossing over to a single 400-mg albaconazole tablet. Another 20 participants took the formulations in reverse order. The total duration of the treatment and follow-up periods was 44–46 days.

Before participants were randomized for treatment, inclusion and exclusion criteria and study protocols were reviewed; participants signed the informed consent document; demographic information and participant medical histories were obtained; physical examinations were conducted; vital signs were measured; and body mass index values were calculated. Additionally, during the screening period, the following tests were performed: clinical laboratory tests (chemistry, hematology, and urinalysis); a serum pregnancy test; a urine drug screen; an alcohol screen; a 12-lead ECG; a concomitant medication query; and screening tests for the human immunodeficiency virus, hepatitis B surface antigen and hepatitis B core antibodies, and the anti-hepatitis C virus. Clinical laboratory tests, physical examinations, and serum pregnancy tests were also performed on days −1 and 16 of the first dose period, and on day −1 and day 16 of the second dose period.

A 12-lead ECG was recorded during screening and on days −1, 1 (pre-dose and ≥3 hours after dosing), and 16 of both dose periods. Vital signs were taken during screening; on days −1, 1, 2, and 16 of the first dose period and on days −1, 1, 2 and 16 of the second dose period. Blood samples for PK testing were obtained at the following time points during each dose period: pre-dose; at 30 minutes; and at hours 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12 (day 1 time points), 18 (day 2), 24 (day 2), 48 (day 3), 72 (day 4), 96 (day 5), 120 (day 6), 144 (day 7), 168 (day 8), 192 (day 9), 216 (day 10), 240 (day 11), 264 (day 12), 288 (day 13), 312 (day 14), 336 (day 15), and 360 (day 16) after dosing. Participants were discharged from the facility on day 2 of both dose periods following the 24-hour PK blood sampling. Concomitant medication information was obtained at every visit and AEs were assessed at every visit after screening. A schematic of the study design is shown in Figure 1.

This study was approved by the IntegReview Ethical Review Board (Austin, TX, USA) and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Study objectives

The primary objective of this study was to compare the bioavailability of a single 400-mg tablet of albaconazole with four 100-mg capsules. The secondary objectives were to assess the bioequivalence between albaconazole tablets and capsules and the safety and tolerability of a single 400-mg oral dose of albaconazole when given as a tablet.

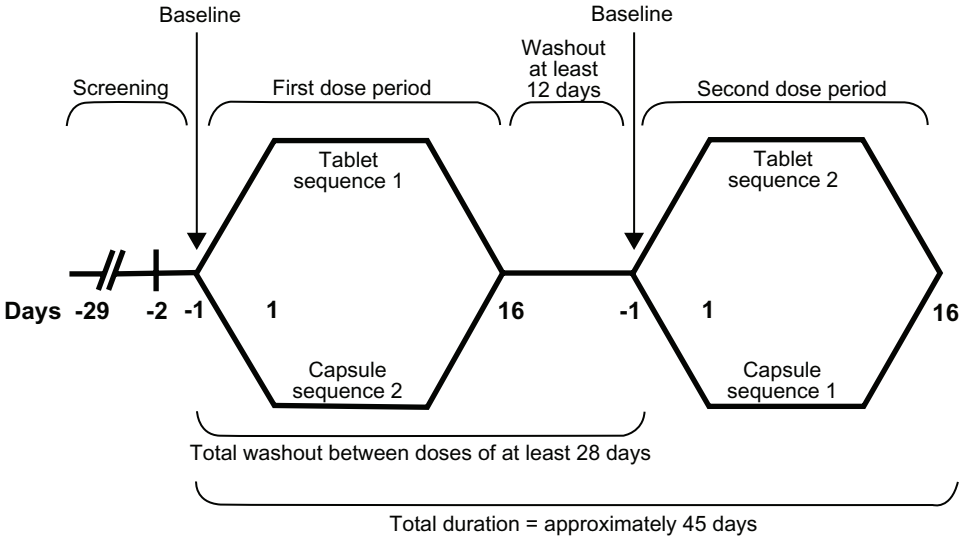

Figure 1 Schematic of the study design.

Concentration, PK, and statistical analysis

Albaconazole and 6-hydroxyalbaconazole were analyzed by liquid chromatography-tandem mass spectrometry; internal standards were albaconazole-d5 and 6-hydroxyalbaconazole-d5. The method was found to produce linear calibration curves for albaconazole and 6-hydroxyalbaconazole over the range 1.000–1000 ng/mL plasma for both analytes. The accuracy (−5.6% to 4.3% for albaconazole and −7.6% to 0.1% for 6-hydroxyalbaconazole) and precision (3.1% to 5.1% for albaconazole and 4.1% to 6.5% for 6-hydroxyalbaconazole) of the method over the range of the assay was found to be acceptable.

The PK analysis set consisted of all participants who received at least one dose of the study product and had adequate blood sampling to calculate PK parameters. The following PK parameters were calculated by noncompartmental methods with the WinNonlin software (Pharsight Corporation, Mountain View, CA, USA) using the PK-evaluable analysis data set: (1) the maximum measured plasma concentration (C_{max}), (2) the time of the maximum measured plasma concentration (T_{max}), (3) the area under the plasma concentration time curve from time 0 (time of dosing) to the last time point with measureable analyte concentrations (AUC_{0-t}), (4) the area under the plasma concentration time curve from time 0 (time of dosing) to infinity (AUC_{0-inf}), (5) the percentage of the extrapolated area under the plasma concentration time curve (%AUC_{ext}), and (6) the apparent first-order terminal elimination half-life ($t_{1/2}$) where determinable. PK parameters were summarized by study formulation. The geometric mean and associated 95% confidence interval (CI) were calculated for all PK parameters except T_{max} and %AUC_{ext}.

An analysis of variance was performed on the natural logarithm (ln)-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} for comparison between albaconazole in the test treatment (tablet) and albaconazole in the reference treatment (capsule). Ratios of least-square (LS) means were calculated using the exponentiation of the LS from the analyses of the natural logarithm-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}. Additionally, 90% CIs for the LS mean ratios were calculated.

The safety analysis set included all participants who received at least one dose of the study product. Safety variables were assessed throughout the course of the study and included AEs; clinical laboratory evaluations; 12-lead ECG results; physical examinations; and vital signs. For AEs, frequencies and percentages were presented overall, for each system organ class, and for each preferred term. An AE was assigned to the study formulation received in the first dose period if the AE occurred after drug administration in the first dose period and prior to taking the study formulation in the second dose period. An AE was assigned to the study formulation received in the second dose period if the AE occurred after drug administration in the second dose period. For ECG analysis, summary statistics were presented by study formulation for observed data and for changes from the baseline for each scheduled visit and time point for PR; RR; QRS; QT; Bazett's correction for QT interval (QTcB); and Fridericia's correction for QT interval (QTcF). Summary statistics for clinical laboratory tests and vital signs were presented by study formulation for observed data and for changes from the baseline for each scheduled visit.

Results

Study participants

Forty participants were enrolled in the study and exposed to the study product. Thirty-eight (95%) completed the study and two (5%) discontinued the study, one (2.5%) due to an AE and the other due to a family emergency (Table 1). The mean age in the safety analysis set was 26.4 years, with a range of 18–44 years. Approximately 58% of the participants were female, 52.5% of the participants were black, and 22.5% of the participants were Hispanic or Latino (Table 2).

Plasma albaconazole and 6-hydroxyalbaconazole exposure and PK parameters

The mean C_{max} of albaconazole was approximately 22% lower after intake of the tablet formulation than after intake of the capsule formulation (Table 3). The median T_{max} for albaconazole was observed at 3.4 hours after administration for the tablet and 3.3 hours for the capsule. The plasma concentration thereafter declined biexponentially, with an initial rapid phase followed by a shallower elimination phase, with an average $t_{1/2}$ of about 80 hours for both formulations (Table 3 and Figure 2A). However, a large intersubject variability was observed for the $t_{1/2}$, with individual values ranging

Table 1 Study participant disposition

Disposition	Number (%) of participants
Enrolled	40
Exposed to study product	40 (100)
Completed	38 (95)
Discontinued	2 (5)
Reason for discontinuation	
AEs	1 (3)
Other	1 (3)

Abbreviation: AE, adverse event.

Table 2 Study participant demographics

Age, years	
N	40
Mean (SD)	26.4 (7.1)
Median (min, max)	24.5 (18, 44)
Sex, n (%)	
Male	17 (42.5)
Female	23 (57.5)
Race, n (%)	
Black	21 (52.5)
White	19 (47.5)
Ethnicity, n (%)	
Hispanic or Latino	9 (22.5)
Not Hispanic or Latino	31 (77.5)
Baseline weight, kg	
N	40
Mean (SD)	70.2 (11.15)
Median (min, max)	67.6 (46.3, 93.0)
Baseline height, cm	
N	40
Mean (SD)	168.1 (8.69)
Median (min, max)	167.6 (154.9, 185.4)
Baseline BMI, kg/m^2	
N	40
Mean (SD)	24.3 (2.7)
Median (min, max)	24 (19, 30)

Abbreviations: BMI, body-mass index; max, maximum; min, minimum; SD, standard deviation.

from 21 to 258 hours across the two formulations. The mean albaconazole AUC_{0-t} and AUC_{0-inf} with the tablet were 10.5% and 9% lower, respectively, than with the capsule formulation. AUC_{0-t} values also showed high intersubject variability, though to a lesser extent than the $t_{1/2}$ values. The reason for the variability in albaconazole PKs is not known.

The C_{max} and AUC geometric means for 6-hydroxyalbaconazole were also lower for the tablet formulation compared with the capsule formulation (Figure 2B and Table 3). With both formulations, the C_{max} and AUC for 6-hydroxyalbaconazole were consistently lower than for albaconazole. The parent-to-metabolite ratios of geometric means for C_{max}, AUC_{0-t}, and AUC_{0-inf} for albaconazole tablets versus capsules were 7.3:8.9, 2.2:2.3, and 2.0:2.1, respectively. The parent and metabolite half-lives were comparable, suggesting that 6-hydroxyalbaconazole has a potential formation rate-limited clearance.

One subject experienced several episodes of emesis the night before administration of the tablet formulation (second dose period), but no emesis was reported following dosing. This subject appeared to be an outlier; capsule-to-tablet C_{max} and AUC ratios for this subject were 7 and 15, respectively,

Table 3 Pharmacokinetic parameters of albaconazole and 6-hydroxyalbaconazole after 400-mg single-dose administration (PK analysis set)

Statistics	$t_{1/2}$, h	T_{max}, h	C_{max}, ng/mL	AUC_{0-t}, h·ng/mL	AUC_{0-inf}, h·ng/mL	$\%AUC_{ext}$, %
Albaconazole						
Tablet formulation (n = 39)						
Mean	79.3	3.4	1747.2	104,186.1	114,091.7	6.4
SD	51.33	1.88	532.94	45,463.04	56,200.28	8.92
Geometric mean	66.7	–	1651.0	93,322.7	100,173.6	–
Median	64.2	3.5	1670.0	101,151.2	107,796.1	2.3
Min, max	20.9, 258.1	1.0, 12.0	333.0, 2980.0	10,486.5, 228,266.5	10,533.3, 285,450.4	0, 39.7
Capsule formulation (n = 39)						
Mean	76.6	3.3	2246.8	116,482.6	125,398.8	6.0
SD	50.34	1.33	825.00	47,726.50	53,499.29	8.01
Geometric mean	64.1	–	2085.6	107,436.7	114,793.8	–
Median	57.7	3.5	2350.0	111,316.9	114,472.3	2.0
Min, max	22.6, 255.5	1.0, 6.0	781.0, 3890.0	48,433.5, 246,639.0	50,632.9, 248,624.2	0, 35.4
6-hydroxyalbaconazole						
Tablet formulation (n = 39)						
Mean	98.4	96.2	247.9	47,742.0	54,614.3	12.2
SD	71.70	49.47	108.91	20,607.96	22,154.60	13.03
Geometric mean	78.5	–	225.4	42,757.5	48,945.5	–
Median	72.3	72.1	235.0	43,881.8	53,474.6	6.0
Min, max	28.4, 324.8	8.0, 240.0	75.0, 580.0	7,673.8, 106,246.2	7,725.5, 107,988.7	0.2, 44.0
Capsule formulation (n = 39)						
Mean	95.3	106.5	262.8	49,999.1	59,374.6	12.1
SD	83.13	53.32	131.71	19,169.32	30,557.21	14.43
Geometric mean	74.0	–	233.7	46,347.6	53,633.1	–
Median	67.1	96.0	226.0	45,867.2	51,216.1	7.0
Min, max	22.7, 385.8	24.0, 240.0	68.8, 607.0	12,412.4, 90,128.4	12,507.0, 198,033.4	0.1, 59.6

Abbreviations: $\%AUC_{ext}$, percentage of the extrapolated area under the plasma concentration time curve; AUC_{0-inf}, area under the plasma concentration time curve from time 0 (time of dosing) to infinity; AUC_{0-t}, area under the plasma concentration time curve from time 0 to the last measurable concentration; C_{max}, maximum measured plasma concentration; max, maximum; min, minimum; PK, pharmacokinetics; SD, standard deviation; $t_{1/2}$, apparent first-order terminal elimination half-life; T_{max}, time of the maximum measured plasma concentration.

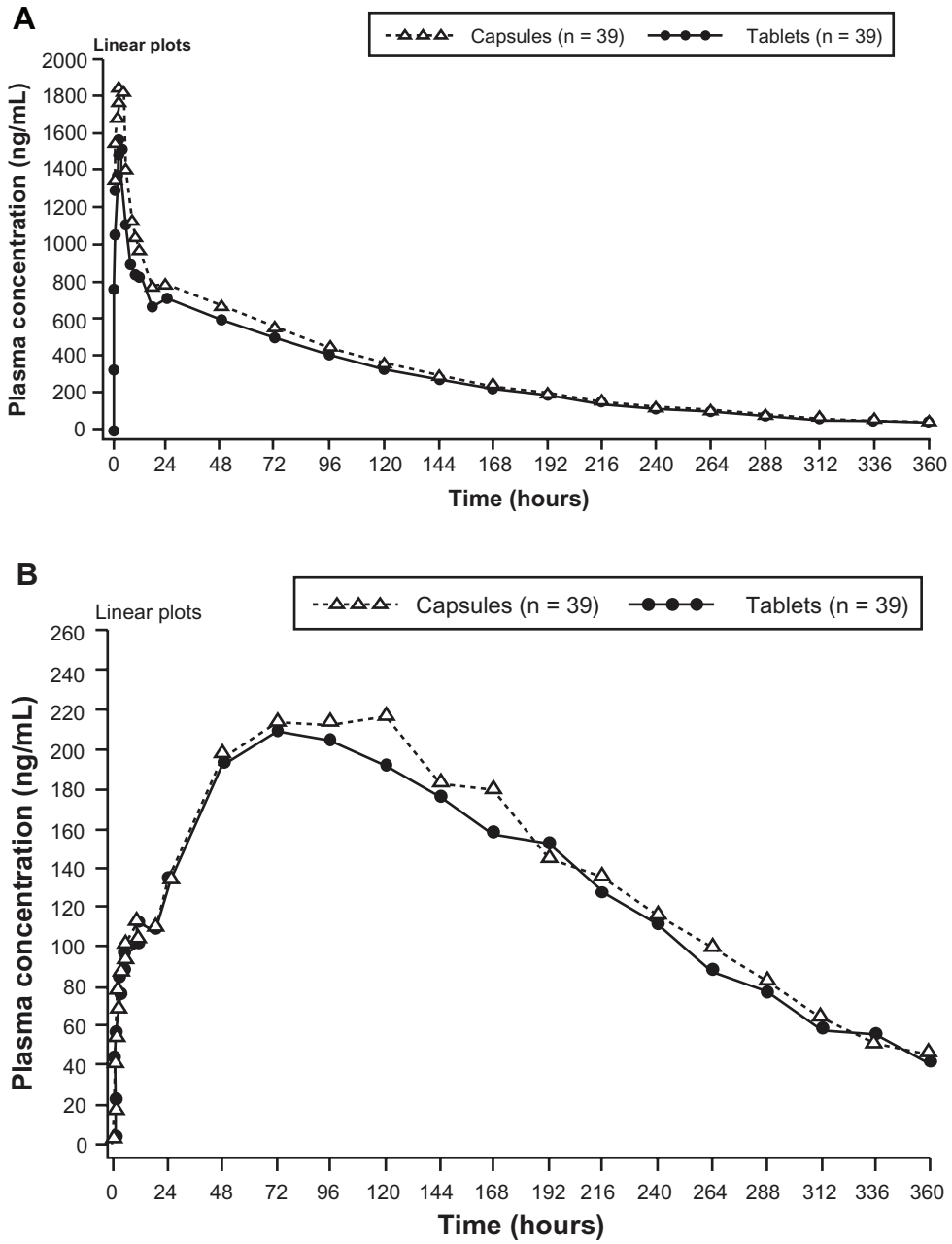

Figure 2 Mean albaconazole (**A**) and 6-hydroxyalbaconazole (**B**) plasma concentrations versus time curves for all participants (PK analysis set).

whereas they ranged from 0.5 to 2.75 in the rest of the participants (Table 4).

ANOVA of selected PK parameters

The geometric mean of the C_{max} for the tablet formulation of albaconazole was 79% of that of the capsule formulation; this difference reached statistical significance (Table 5). The differences in the geometric means for the AUC between the formulations did not reach statistical significance ($P > 0.05$). The 90% CIs based on the difference between the albaconazole tablet and capsule formulations were outside the 80%–125% range for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}. It can therefore be concluded that the two formulations are not bioequivalent with regard to the extent (AUC) or the rate (C_{max}) of absorption. When the subject who repeatedly experienced emesis before dosing was excluded from the analysis, the average C_{max} was still statistically significantly lower for the tablet formulation, and the two formulations were not bioequivalent with regard to C_{max} (90% CI 75%–91.5%). However, the 90% CI for $AUC_{0\text{-}t}$ (86.5%–101.4%) and $AUC_{0\text{-}inf}$ (86.5%–102.3%) were contained within the 90% CI bioequivalence range (80%–125%), and the two formulations

Table 4 Pharmacokinetic parameters of albaconazole and 6-hydroxyalbaconazole after 400-mg single-dose administration, excluding subject 41 (PK analysis set)

Statistics	$t_{1/2}$, h	T_{max}, h	C_{max}, ng/mL	AUC_{0-t}, h·ng/mL	AUC_{0-inf}, h·ng/mL	$\%AUC_{ext}$, %
Albaconazole						
Tablet formulation (n = 38)						
Mean	80.8	3.2	1784.4	106,651.9	116,816.9	6.5
SD	51.10	1.26	486.04	43,349.95	54,280.39	8.99
Geometric mean	68.8	–	1722.0	98,848.6	106,290.7	–
Median	64.8	3.3	1685.0	101,649.9	108,467.7	2.4
Min, max	25.1, 258.1	1.0, 8.0	976.0, 2980.0	38,206.4, 228,266.5	38,276.9, 285,450.5	0, 39.7
Capsule formulation (n = 38)						
Mean	78.0	3.3	2242.3	115,319.3	124,469.0	6.2
SD	50.25	1.35	835.58	47,803.53	53,897.13	8.06
Geometric mean	65.8	–	2077.5	106,304.6	113,781.5	–
Median	58.5	3.4	2335.0	108,512.2	114,321.3	2.0
Min, max	22.6, 255.5	1.0, 6.0	781.0, 3890.0	48,433.5, 246,639.0	50,632.9, 248,624.2	0, 35.4
6-hydroxyalbaconazole						
Tablet formulation (n = 38)						
Mean	100.3	97.5	252.2	48,796.4	55,881.6	12.5
SD	71.73	49.48	106.96	19,789.73	21,017.58	13.07
Geometric mean	80.7	–	231.3	44,734.6	51,449.6	–
Median	72.5	84.1	238.0	45,019.1	54,290.9	6.6
Min, max	30.3, 324.8	8.0, 240.0	75.0, 580.0	13,052.5, 106,246.2	13,493.0, 107,988.7	0.2, 44.0
Capsule formulation (n = 38)						
Mean	97.0	104.9	261.2	49,865.5	59,483.8	12.4
SD	83.55	53.05	133.09	19,408.25	30,959.69	14.49
Geometric mean	75.7	–	231.7	46,137.7	53,591.9	–
Median	67.1	96.0	223.5	45,301.6	51,157.9	7.5
Min, max	22.7, 385.8	24.0, 240.0	68.8, 607.0	12,412.4, 90,128.4	12,507.0, 198,033.4	0.1, 59.6

Abbreviations: $\%AUC_{ext}$, percentage of the extrapolated area under the plasma concentration time curve; AUC_{0-inf}, area under the plasma concentration time curve from time 0 (time of dosing) to infinity; AUC_{0-t}, area under the plasma concentration time curve from time 0 to the last measurable concentration; C_{max}, maximum measured plasma concentration; max, maximum; min, minimum; PK, pharmacokinetics; SD, standard deviation; $t_{1/2}$, apparent first-order terminal elimination half-life; T_{max}, time of the maximum measured plasma concentration.

could be considered bioequivalent with regard to the extent of absorption.

Safety

Both formulations of albaconazole were generally well-tolerated. An overview of AEs reported in the safety analysis sets is reported in Table 6. All AEs were mild in intensity. The most common AEs reported were gastrointestinal disorders (in 10% of the participants given an albaconazole tablet versus 23% of participants given a capsule formulation). Two participants (5.1%) in the tablet group and seven participants (17.9%) in the capsule group had gastrointestinal AEs that were considered to be related to the study product. No serious AEs or deaths were reported. One subject was withdrawn from the study as a result of an AE (urinary tract infection) considered unrelated to the study treatment.

Changes from the baseline in laboratory measurements were small and variable following the administration of the study product. No clinically relevant changes were seen in individual participants. There were also no clinically relevant changes from the baseline in vital signs, and no vital sign measurement was reported as an AE. Mean changes from the baseline in ECG measurements were minimal and similar across treatment groups. No subject in either group had a QTcB or QTcF interval ≥ 450 ms for any visit, and no participants had ECG findings reported as an AE.

Discussion

This study compared the bioavailability and bioequivalence of albaconazole tablets with albaconazole capsules. Exposure to albaconazole and 6-hydroxyalbaconazole after a single 400-mg dose of albaconazole was higher with the capsule formulation than with the tablet formulation. This difference in albaconazole was not statistically significant for the AUC, but reached statistical significance for the C_{max}. The two formulations were not bioequivalent with regard to the extent (AUC) or the rate (C_{max}) of absorption. Systemic exposure to 6-hydroxyalbaconazole, as measured by AUC and C_{max}, was consistently lower for both formulations when compared to albaconazole. When the subject

Table 5 Analysis of variance of selected albaconazole PK parameters for all participants (PK analysis set)

Parameter	Statistic	Tablet versus capsule
AUC_{0-inf}, hr · ng/mL	Geometric LS mean ratio	87.46
	90% CI for geometric LS mean ratio	(75.8–100.9)
	P value	0.1222
AUC_{0-t}, hr · ng/mL	Geometric LS mean ratio	87.04
	90% CI for geometric LS mean ratio	(75.6–100.2)
	P value	0.1046
C_{max}, ng/mL	Geometric LS mean ratio	79.04
	90% CI for geometric LS mean ratio	(69.7–89.6)
	P value	0.0032

Abbreviations: AUC_{0-inf}, area under the plasma concentration time curve from time 0 (time of dosing) to infinity; AUC_{0-t}, area under the plasma concentration time curve from time 0 to the last measurable concentration; CI, confidence interval; C_{max}, maximum measured plasma concentration; LS, least squares; PK, pharmacokinetics.

Table 6 Incidence of treatment-emergent adverse events classified by system organ class and preferred term (safety analysis set)

System organ class/preferred term	Formulation	
	Tablet (n = 39)	Capsule (n = 39)
Participants reporting any AE, n (%)	11 (28)	13 (33)
Eye disorders, n (%)	0	1 (3)
Eye swelling	0	1 (3)
Gastrointestinal disorders, n (%)	4 (10)	9 (23)
Abdominal pain	0	1 (3)
Upper abdominal pain	1 (3)	0
Constipation	1 (3)	1 (3)
Dyspepsia	0	1 (3)
Nausea	2 (5)	6 (15)
Vomiting	2 (5)	0
Infections and infestations, n (%)	1 (3)	1 (3)
Nasopharyngitis	1 (3)	1 (3)
Urinary tract infection	1 (3)	0
Injury, poisoning, and procedural complications, n (%)	1 (3)	1 (3)
Excoriation	1 (3)	0
Joint injury	0	1 (3)
Musculoskeletal and connective tissue disorders, n (%)	1 (3)	0
Musculoskeletal pain	1 (3)	0
Nervous system disorders, n (%)	4 (10)	5 (13)
Dizziness	1 (3)	2 (5)
Headache	3 (8)	4 (10)
Psychiatric disorders	0	1 (3)
Abnormal dreams	0	1 (3)
Reproductive system and breast disorders	1 (3)	0
Dysmenorrhea	1 (3)	0
Respiratory, thoracic, and mediastinal disorders	2 (5)	0
Oropharyngeal pain	1 (3)	0
Throat irritation	1 (3)	0

Abbreviation: AE, adverse event.

who repeatedly experienced emesis the night before the intake of albaconazole and was an outlier with respect to PK variables was excluded from the PK analysis set, the results showed that the two formulations can be considered bioequivalent with regard to the extent of absorption (though the AUC was approximately 8% lower for the tablet [AUC_{0-t} LS mean ratio 93.65; 90% CI, 86.5–101.4]), but not with regard to the rate of absorption (the C_{max} was approximately 20% lower for the tablet [LS mean ratio 82.83; 90% CI, 75–91.5; $P < 0.003$]).

In both capsule and tablet formulations, 400-mg albaconazole was safe and well-tolerated by healthy participants. All AEs were mild, no serious AEs or deaths occurred, and no laboratory measurements, vital signs, or ECG findings were reported as AEs. One subject withdrew from the study as a result of a medication used to treat an AE (although the withdrawal was recorded as being due to a urinary tract infection), which was considered to be unrelated to the study product. The system organ class with the largest number of AEs (10% for albaconazole tablets versus 23% for the capsule formulation) was gastrointestinal disorders.

A dose-finding study in distal subungual toenail onychomycosis has demonstrated that once-weekly oral doses of 100–400 mg albaconazole (taken as four 100-mg capsules) for 24 or 36 weeks resulted in high rates of clinical and mycological resolution. The response was dose-dependent, and it was postulated that higher rates of clinical and mycological resolution could possibly be achieved with increased dose amounts or treatment durations (Stiefel, unpublished data). When developing a formulation for therapeutic dosing, it is clear that the oral intake of one tablet would be preferable over four or more capsules for most patients. Taking into account the observed lower bioavailability of albaconazole from the tablet formulation used in this study, further studies may be required to assess whether a higher dose may be needed in a tablet formulation to obtain the same systemic exposure, and therefore potentially the same therapeutic effect, as capsules.

Conclusion

The AUC and C_{max} of albaconazole after a single 400-mg oral dose administered as a tablet formulation were lower than those of the capsule formulation. The two formulations were not bioequivalent with regard to the extent (AUC) or rate of absorption (C_{max}). In both tablet and capsule formulations, 400-mg albaconazole was safe and well-tolerated by the healthy participants in this study.

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Disclosure

Both Dr van Rossem and Jennifer Lowe are employees of Stiefel. The authors report no other conflicts of interest in this work.

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