A new solid oral tablet formulation of posaconazole: a randomized clinical trial to investigate rising single- and multiple-dose pharmacokinetics and safety in healthy volunteers

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Objectives: Posaconazole is an extended-spectrum triazole with proven efficacy as antifungal treatment and prophylaxis. The marketed oral suspension should be taken with food to maximize systemic absorption. A new solid oral tablet has been developed with improved bioavailability that can be administered without regard to food. The aim of this study was to evaluate rising single- and multiple-dose pharmacokinetics, safety and tolerability of the new tablet.

Methods: This was a single-centre, randomized, placebo-controlled, Phase I, rising single- and multiple-dose study of healthy subjects aged 18–65 years who received a posaconazole tablet as 200 mg once daily, 200 mg twice daily or 400 mg once daily. The 24 subjects were studied in two cohorts of 12 subjects each (9 active and 3 placebo).

Results: After single or multiple oral dose administration of posaconazole tablets (200 and 400 mg), exposure increased in a dose-related manner. Peak posaconazole concentrations were attained at a median T\text{max} of 4–5 h. Mean half-life was similar for 200 and 400 mg posaconazole doses (25 and 26 h). The accumulation ratio upon multiple doses over 8 days was ≈3 for 200 and 400 mg once daily and ≈5 for 200 mg twice daily. C\text{avg} values exceeded 1300 ng/mL. The posaconazole oral tablet was safe and well tolerated, although mild, transient elevations in liver function were reported in some patients.

Conclusions: Posaconazole exposure increased in a dose-related manner. The pharmacokinetics of this new solid oral tablet of posaconazole supports the clinical evaluation of once-daily dosing regimens for fungal infections.

Keywords: exposure, absorption, once-daily dosing

Introduction

Posaconazole is an extended-spectrum triazole with demonstrated efficacy as prophylaxis for invasive fungal disease (IFD) and as treatment for refractory IFD. The bioavailability of posaconazole oral suspension is significantly enhanced when coadministered with food, and it is therefore prescribed with food to maximize systemic absorption. Bioavailability may also be enhanced by dividing doses or by administering the drug with a liquid nutritional supplement or acidic beverage.

A new solid oral tablet with improved bioavailability has been developed that can be administered without regard to food. The tablet is designed to release the entire dose of solubilized posaconazole in the small intestine, maximizing systemic absorption. In an exploratory study, this new solid oral formulation significantly increased exposure to posaconazole relative to the oral suspension in fasting healthy volunteers. Since many patients taking posaconazole are unable to tolerate food, the ability to attain a higher exposure in a fasted state with this new solid oral formulation could reduce dose frequency in patients from two or three times a day to a once-daily regimen independent of food.

The primary objective of this study was to evaluate the rising single- and multiple-dose pharmacokinetics of posaconazole for the new tablet formulation. The safety and tolerability of the tablet formulation were also assessed.
Methods

Study design

This was a single-centre, randomized, placebo-controlled, Phase I, rising single- and multiple-dose study. The study took place between 19 March 2009 and 20 May 2009 at the Clinical Pharmacology Research Unit, University of Miami, Miami, FL, USA.

Subjects and treatments

The study protocol was approved by the University of Miami Human Subjects Research Office. The study was conducted in accordance with the principles of Good Clinical Practice. Written informed consent was obtained from each patient before enrolment.

Healthy male and female participants aged 18–65 years with a body mass index of 19–35 kg/m² were enrolled. Initially, 24 subjects were planned to participate. It was decided, after consultation between the sponsor and principal investigator, that enrolment could be extended to include replacement of subjects who discontinued while on study. Subjects were required to have clinical laboratory test results (haematology, blood chemistry and urinalysis) within normal limits or clinically acceptable to the investigator/sponsor. Female subjects were either postmenopausal, surgically sterilized (with a negative pregnancy test at screening and at each admission to the study centre), or premenopausal, unsterilized using a medically accepted method of contraception or abstaining from sexual intercourse from 2 months prior to study entry to 2 months after stopping study medication. Male subjects agreed to use a medically accepted method of contraception or agreed to abstain from sexual intercourse during the study and for 1 month after stopping the study drug. Subjects were required not to have had any surgical or medical condition that might significantly alter the absorption, distribution, metabolism or excretion of any drug. Subjects were excluded if they had a history of any infectious disease within 4 weeks prior to drug administration, a positive result for hepatitis B surface antigen, hepatitis C antibodies, HIV or drug use with a high potential for abuse. Subjects were excluded if they had a history of alcohol or drug abuse in the past 2 years, concomitant use of medications (including over-the-counter medicines, vitamin supplements or herbal remedies) that might significantly alter the absorption, distribution, metabolism or excretion of any drug. Subjects were excluded if they had a history of any infectious disease within 4 weeks prior to drug administration, a positive result for hepatitis B surface antigen, hepatitis C antibodies, HIV or drug use with a high potential for abuse. Subjects were excluded if they had a history of alcohol or drug abuse in the past 2 years, concomitant use of medications (including over-the-counter medicines, vitamin supplements or herbal remedies) that might significantly alter the absorption, distribution, metabolism or excretion of any drug. Subjects were excluded if they had a history of alcohol or drug abuse in the past 2 years, concomitant use of medications (including over-the-counter medicines, vitamin supplements or herbal remedies) that might significantly alter the absorption, distribution, metabolism or excretion of any drug.

Posaconazole tablets contained 100 mg of posaconazole in a solid dispersion formed by dissolving posaconazole in a pH-sensitive polymer matrix using hot-melt extrusion technology. The drug substance was dispersed in a carrier matrix using hot-melt extrusion technology. The drug substance was dispersed in a carrier matrix using hot-melt extrusion technology. The drug substance was dispersed in a carrier matrix using hot-melt extrusion technology. The drug substance was dispersed in a carrier matrix using hot-melt extrusion technology. The drug substance was dispersed in a carrier matrix using hot-melt extrusion technology.

Subjects were randomized according to a computer-generated sponsor-provided randomization code to receive single and multiple doses of either posaconazole (9 subjects) or matching placebo (3 subjects) (Figure 1). Treatment was prepared according to the randomization schedule and dispensed in a blinded fashion by a third party who was not involved in any study procedures, assessments or data recording. Placebo tablets were identical to the posaconazole tablets and were prepared according to the randomization schedule and dispensed in a blinded fashion by a third party who was not involved in any study procedures, assessments or data recording. Placebo tablets were identical to the posaconazole tablets and were prepared according to the randomization schedule and dispensed in a blinded fashion by a third party who was not involved in any study procedures, assessments or data recording. Placebo tablets were identical to the posaconazole tablets and were prepared according to the randomization schedule and dispensed in a blinded fashion by a third party who was not involved in any study procedures, assessments or data recording. Placebo tablets were identical to the posaconazole tablets and were prepared according to the randomization schedule and dispensed in a blinded fashion by a third party who was not involved in any study procedures, assessments or data recording. Placebo tablets were identical to the posaconazole tablets and were prepared according to the randomization schedule and dispensed in a blinded fashion by a third party who was not involved in any study procedures, assessments or data recording.

Blood samples were collected at the following pre-determined time-points for both cohorts: day 1: 0 h (pre-dose) and at 2, 3, 4, 5, 6, 8, 12, 24, 48, 72 and 120 h post-dose; day 6: at 2, 3, 4, 5, 6, 8, 12, 24 and 24 h post-dose; and pre-dose (trough level) samples on days 12 and 13. Additional samples for Cohort 1 were taken on day 14: 0 h (pre-dose) and at 2, 3, 4, 5, 6, 8, 12 and 24 h post-dose; and day 22: 0 h (pre-dose) and at 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 72, 120 and 168 h post-dose. Additional samples for Cohort 1 were taken on day 14: 0 h (pre-dose) and at 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 72, 120 and 168 h post-dose. Additional samples for Cohort 2 were taken on day 14: 0 h (pre-dose) and at 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 72, 120 and 168 h post-dose. Additional samples for Cohort 2 were taken on day 14: 0 h (pre-dose) and at 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 72, 120 and 168 h post-dose.

Plasma samples were isolated and assayed for posaconazole using validated liquid chromatography with tandem mass spectrometric detection with a calibrated range of 5–5000 ng/mL, precision of 2.0%–6.6% and accuracy of –11.8% to 3.3%.

The primary pharmacokinetic variables assessed were: AUC0–24 (AUC0–τ), during the dosing interval (AUCD), and from time 0 to the time of the final quantifiable sample (AUCQ); maximum plasma concentration (Cmax); time to Cmax (tmax); apparent total body clearance (CL/F); and terminal-phase half-life (t1/2). For the multiple-dose part, average plasma concentration over the dosing interval (Cavg) and accumulation ratio (R) were also calculated. Summary statistics (means, standard deviations and coefficients of variation (%CV) were calculated. Derived log-transformed, dose-normalized pharmacokinetic parameters (AUCD/Q and Cavg) were statistically analysed for a preliminary assessment of

Figure 1. Study design. BID, twice daily; QD, once daily; POS, posaconazole; SD, single dose.
dose proportionality across subjects. Dose-normalized AUC values were scaled from mean values for 200 and 400 mg. Assessment of dose proportionality was based on ratios (between doses) of model adjusted geometric means for AUC ($C_{\text{max}}$) and corresponding 90% CIs using day 14 data. The determination of sample size (12 subjects per cohort) was based on empirical rather than statistical considerations.

**Safety analyses**

Safety assessments (vital signs, physical examination, ECGs and clinical laboratory tests) were conducted for both cohorts on days −1, 6 and 10, and additionally on days 23 and 29 (Cohort 1) or days 15 and 21 (Cohort 2). Adverse events (AEs) were assessed throughout the study.

**Results**

**Subject demographics and disposition**

Of 25 subjects enrolled in this study, 13 (including a replacement subject) were in Cohort 1 (10 posaconazole and 3 matching placebo) and 12 were in Cohort 2 (9 posaconazole and 3 matching placebo) (Table 1). All subjects were white and of Hispanic or Latino ethnicity, aged between 31 and 59 years (mean age 45.9 years), and 14 subjects (56%) were male. A total of 22 out of 25 subjects completed the study (3 subjects were discontinued due to AEs). All 19 subjects who received at least one dose of posaconazole were included in the pharmacokinetic analyses; placebo subjects were excluded from the pharmacokinetic analyses.

**Pharmacokinetics**

After single oral administration of posaconazole tablets (200 or 400 mg), exposure between groups differed in an approximately dose-proportional manner (Table 2). Plasma concentration–time profiles are shown for days 1 and 14 (Figure 2). Mean $t_{1/2}$ values after a single administration were similar for 200 and 400 mg doses (~25 and 26 h, respectively), while peak concentrations were attained at a median $T_{\text{max}}$ of 4 h (200 mg) and 5 h (400 mg). Based on log-transformed data, the dose-normalized $C_{\text{max}}$ and AUC$_{\text{tf}}$ for 400 mg were 83% and 91%, respectively, of those observed with the 200 mg dose on day 1 (Table 3).

Following multiple oral administration of posaconazole tablet (200 mg once daily, 200 mg twice daily or 400 mg once daily) for 8 days, the exposure among treatment groups increased in a dose-related manner (Table 4). The accumulation ratio upon multiple doses was ~3 for 200 and 400 mg once daily and ~5

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**Table 1. Subject demographics**

|                      | Cohort 1 (200 mg of posaconazole), n=10 | Cohort 2 (400 mg of posaconazole), n=9 | Placebo, n=6 | All subjects, n=25 |
|----------------------|----------------------------------------|----------------------------------------|--------------|-------------------|
| Gender, male, n (%)  | 5 (50)                                 | 6 (67)                                 | 3 (50)       | 14 (56)           |
| Race, n (%)          |                                        |                                        |              |                   |
| White                | 10 (100)                               | 9 (100)                                | 6 (100)      | 25 (100)          |
| Ethnicity, n (%)     |                                        |                                        |              |                   |
| Hispanic or Latino   | 10 (100)                               | 9 (100)                                | 6 (100)      | 25 (100)          |
| Age, years           |                                        |                                        |              |                   |
| mean (SD)            | 47.7 (8.2)                             | 43.8 (9.9)                             | 46.0 (9.3)   | 45.9 (8.9)        |
| median (range)       | 46.5 (33–59)                           | 40.0 (31–56)                           | 46.5 (33–56) | 44.0 (31–59)      |
| Weight, kg           |                                        |                                        |              |                   |
| mean (SD)            | 74.85 (14.13)                          | 72.89 (7.61)                           | 71.83 (9.58) | 73.42 (10.72)     |
| median (range)       | 71 (61–100)                            | 72 (61–86)                             | 71 (61–88)   | 71 (61–100)       |
| Height, cm           |                                        |                                        |              |                   |
| mean (SD)            | 165.60 (5.62)                          | 168.78 (7.90)                          | 166.17 (8.18) | 166.88 (6.98)    |
| median (range)       | 165 (156–175)                          | 168 (155–181)                          | 167 (153–175)| 167 (153–181)    |

**Table 2. Mean (%CV) of posaconazole pharmacokinetic parameters after single oral tablet administration of 200 or 400 mg of posaconazole**

| Dose (mg) | Day | n  | $C_{\text{max}}$ (ng/mL) | $T_{\text{max}}$ (h) | AUC$^{0}_{{\text{tau}}}$ (ng.h/mL) | AUC$^{0}_{{\text{tf}}}$ (ng.h/mL) | CL/F (L/h) | $t_{1/2}$ (h) |
|-----------|-----|----|--------------------------|----------------------|------------------------------------|-----------------------------------|------------|---------------|
| 200 mg (Cohort 1) | 1   | 10 | 778 (29)                 | 4.0 (3–8)            | 10500 (23)                         | 23000 (23)                        | 8.80 (26)  | 25.1 (20)    |
| 200 mg (Cohort 1) | 1   | 9  | 1290 (29)                | 5.0 (3–8)            | 18900 (34)                         | 42800 (35)                        | 9.55 (34)$^c$ | 26.1 (22)$^c$ |

$^a$Median (range).

$^b$tau = 24 h.

$^c$n = 8.
for 200 mg twice daily (Table 4). Accumulation appeared to be independent of dose, but as expected was dependent on the dosing regimen (once daily versus twice daily). Inter-subject AUC variability in exposure for 400 mg once daily was relatively high, compared with that for 200 mg once daily (CV, 54% and 32%, respectively).

Based on log-transformed day 14 data, the dose-normalized $C_{\text{max}}$ and $\text{AUC}_{\text{tau}}$ for 400 mg of posaconazole were 76% and 81%, respectively, of those observed with the 200 mg dose following multiple oral administration (Table 3). $C_{\text{avg}}$ (%CV) values are presented in Table 4. Steady-state posaconazole trough concentrations appeared to be achieved after 7 days of multiple dosing in subjects from day 6 to 12 (Figure 3).

### Safety assessments

Posaconazole tablets were generally safe and well tolerated. No serious AEs were reported. Twelve subjects (48%) reported at least one treatment-emergent AE: 6 subjects (60%) treated with 200 mg of posaconazole once daily/twice daily; 5 subjects (56%) treated with 400 mg of posaconazole once daily/twice daily; and 1 subject (17%) in the placebo group. Eleven subjects (44%) reported treatment-related AEs (Table 5): 6 subjects (60%) treated with 200 mg of posaconazole once daily/twice daily; 4 subjects (44%) treated with 400 mg of posaconazole once daily/twice daily; and 1 subject (17%) in the placebo group. The most commonly reported treatment-related AEs were mild increase in hepatic enzyme level [6 subjects (24%)], diarrhoea [3 subjects (12%)] and headache [2 subjects (8%)].

All other treatment-related AEs occurred in only 1 subject each. The mild, transient increases in liver enzyme levels [aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values] were observed in five subjects in the 200 mg of posaconazole once-daily/twice-daily group, and in one subject in the 400 mg of posaconazole once-daily/twice-daily group, after 10 days of treatment. These AEs had no clinical sequelae; however, three of these subjects discontinued treatment with posaconazole (two subjects received 200 mg of posaconazole once daily/twice daily and one subject received 400 mg of posaconazole once daily). Peak AST levels in the three subjects who discontinued treatment were 49, 66 and 73 U/L (reference range, 8–40 U/L). Peak ALT levels in these subjects were 94, 81 and 138 U/L (reference range, 8–54 U/L). In all three subjects, liver enzyme elevations persisted for 1–11 days after posaconazole treatment was discontinued. AST and ALT levels had generally returned to within normal limits by the final study visit. These AEs are consistent with mild, generally reversible liver enzyme elevations previously reported for posaconazole oral suspension.7

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**Table 3.** Statistical analysis of dose-normalized posaconazole (400 versus 200 mg) following single and multiple oral tablet administration

| Day/parameter | Geometric mean ratio (%) | 90% CI       |
|---------------|--------------------------|--------------|
| Day 1         |                          |              |
| $C_{\text{max}}$ | 83                       | 65–106       |
| $\text{AUC}_{\text{tf}}$ | 91                       | 72–114       |
| Day 14        |                          |              |
| $C_{\text{max}}$ | 76                       | 51–114       |
| $\text{AUC}_{\text{tau}}$ | 81                       | 52–126       |

Comparisons were made using a one-way analysis of variance model extracting the effect due to treatment based on log-transformed, dose-normalized data.  

*aModel-based geometric mean ratio.*

**Table 4.** Mean (%CV) of posaconazole pharmacokinetic parameters after multiple oral tablet administration of posaconazole (200 mg once daily, 200 mg twice daily or 400 mg once daily)

| Dose (mg) | Day | n  | $C_{\text{max}}$ (ng/mL) | $T_{\text{max}}$ (h) | $\text{AUC}_{\text{tau}}$ (ng.h/mL) | $C_{\text{avg}}$ (ng/mL) | $R^2$       |
|-----------|-----|----|--------------------------|----------------------|-------------------------------------|--------------------------|------------|
| 200 mg QD (Cohort 1) | 14  | 8  | 1800 (31)                | 5.0 (2–8)            | 31400 (32)                         | 1310 (32)               | 3.14 (24)   |
| 200 mg BID (Cohort 1) | 22  | 8  | 2980 (38)                | 4.0 (2–8)            | 30600 (38)                         | 2550 (38)               | 4.75 (28)   |
| 400 mg QD (Cohort 2)  | 14  | 8  | 2940 (38)                | 5.0 (0–12)           | 56600 (54)                         | 2360 (54)               | 3.16 (57)   |

BID, twice daily; QD, once daily.  

*bMedian (range).*  

$c_{\text{max}}=24$ h for once daily and 12 h for twice daily.  

$c_{\text{avg}}=\text{average concentration}=\frac{\text{AUC}_{\text{tau}}}{\tau}$.  

*C_{\text{tau}}=\text{accumulation ratio}=\frac{\text{AUC}_{\text{tau}}(\text{day 14})}{\text{AUC}_{\text{tau}}(\text{day 1})}.*

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2728
Nausea 0 1 (11) 0 1 (4)
Dry mouth 0 1 (11) 0 1 (4)
Dizziness 1 (10) 0 0 1 (4)
Headache 0 1 (11) 1 (17) 2 (8)
Diarrhoea 0 3 (33) 0 3 (12)

Hepatic enzyme
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This is the first known report of the pharmacokinetics of a new
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tablet in patients.

The results of the current study show that following single
and multiple doses of posaconazole solid oral tablets (200 and
400 mg) in healthy subjects, posaconazole exposure increased
in a dose-related manner. When the dose was increased in a
1:2 ratio, exposure increased in 1:1.9 and 1:1.8 ratios for days
1 and 14, respectively. On day 1, the dose-normalized posacon-
azole exposure (AUC(tau)) value in this study was comparable to
that of the tablet formulation determined in a previous study
(11400 ng-h/mL) and was substantially higher than for the oral
suspension under both fasted and fed conditions (2970 and
8470 ng-h/mL, respectively).3

The half-life of ~1 day predicted attainment of steady state
by day 5–7; this was confirmed by plasma trough concentration
data (Figure 3). A loading dose on day 1 can be utilized for a rapid
attainment of the steady state in cases of serious infections
requiring early effective treatment. The accumulation ratios for
200 and 400 mg once-daily dosing regimens were ~3 and were
not dose-dependent. As expected, the accumulation ratio for
the twice-daily regimen was higher (~5). The half-life for 200
and 400 mg once-daily doses remained unchanged. The apparent
clearance also remained relatively unchanged across doses.

In this study, the posaconazole tablet formulation attained
mean Cavg values >1300 ng/mL at the lowest dose (200 mg
once daily). These values were above average concentration
values associated with efficacy in patients.3 For example, in a
salvage study of patients with refractory invasive aspergillosis,
higher posaconazole plasma concentrations were associated
with higher response rates; a mean posaconazole Cavg of
≥411 ng/mL was associated with a response rate of 53% (versus
26% for a historical control sample), and a 75% response
rate in patients with a mean posaconazole Cavg of ≥1250 ng/mL.3

The positive association between response rate and average con-
centration reinforces the importance of maximizing posacon-
azole exposure in patients at high risk of IFD. These results
further support development of this new solid oral formulation;
Furthermore, it does not have the food requirement that
may limit the utility of the currently marketed oral suspension
formulation in patients with poor food intake.

Mild, asymptomatic increases in liver enzyme values were
observed in five subjects after 10 days of posaconazole treat-
ment. Although elevations observed in the liver function test
were transient and not considered serious or severe, three
subjects discontinued the study due to these AEs. Such transient
elevations in liver function have been previously reported. An
analysis of safety data from 18 clinical pharmacology single-
and multiple-dose trials of posaconazole conducted in healthy
volunteers reported that while posaconazole has the potential
to elevate hepatic enzymes, these changes do not appear to
be exposure-dependent, and most levels returned to baseline
when posaconazole was discontinued.11

There were no clinically significant changes in any other labora-
tory safety parameters, vital signs or ECG results.

Discussion

This is the first known report of the pharmacokinetics of a new
solid oral posaconazole tablet formulation. While extensive clin-
cal safety data for posaconazole are available, this study also
evaluated the safety of this new tablet formulation. The pharmaco-
kinetics data obtained in this study were compared with target
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to elevate hepatic enzymes, these changes do not appear to
be exposure-dependent, and most levels returned to baseline
when posaconazole was discontinued.11

Conclusions

In summary, posaconazole exposures from a new tablet formul-
lization increased in a dose-related manner, with steady-state Cavg
values at the lowest dose (200 mg once daily) exceeding those
previously found to be efficacious against IFD. Accumulation
after multiple dosing was dose-independent. The single- and
multiple-dose pharmacokinetics of this new solid oral tablet of
posaconazole support the clinical evaluation of once-daily
dosing regimens for fungal infections. The posaconazole tablet
at doses of 200 mg, whether administered once or twice daily,
and 400 mg, administered once daily, were generally safe and
well tolerated in healthy subjects.
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Transparency declarations
At the time the study was conducted, G. K. and E. O. were employees and stockholders of Merck Sharp & Dohme Corp. L. M. is a Merck Sharp & Dohme employee and stockholder. M. M. is a Merck Sharp & Dohme employee. R. A. P. has no conflicts of interest to declare.
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Author contributions
G. K. was involved in study conception, design and planning; he also supervised analyses, interpreted results and wrote sections of the initial draft of the manuscript. L. M., M. M. and E. O. performed analyses and interpreted results. R. A. P. was the study principal investigator and was responsible for the conduct of the study, protocol review, participant recruitment, informed consent, safety and data collection and management. All authors critically reviewed the manuscript, providing suggestions for revision where necessary. All authors reviewed and approved the final version of the paper. L. M. and M. M. are guarantors for the data and have full access to the data.

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