
Ketoconazole Increases Fingolimod Blood Levels in a Drug Interaction via CYP4F2 Inhibition

John M. Kovarik, PhD, FCP, Kiran Dole, Gilles-Jacques Riviere, PhD, Francoise Pommier, PhD, Steve Maton, Yi Jin, PhD, Kenneth C. Lasseter, MD, and Robert L. Schmouder, MD

The sphingosine-1-phosphate receptor modulator fingolimod is predominantly hydroxylated by cytochrome CYP4F2. *In vitro* experiments showed that ketoconazole significantly inhibited the oxidative metabolism of fingolimod by human liver microsomes and by recombinant CYP4F2. The authors used ketoconazole as a putative CYP4F2 inhibitor to quantify its influence on fingolimod pharmacokinetics in healthy subjects. In a 2-period, single-sequence, crossover study, 22 healthy subjects received a single 5-mg dose of fingolimod in period 1. In period 2, subjects received ketoconazole 200 mg twice daily for 9 days and a single 5-mg dose of fingolimod coadministered on the 4th day of ketoconazole treatment. Ketoconazole did not affect fingolimod t_{max} or half-life, but there was a weak average increase in C_{max} of 1.22-fold (90% confidence interval, 1.15-1.30). The AUC over the 5 days of ketoconazole coadministration increased

1.40-fold (1.31-1.50), and the full AUC to infinity increased 1.71-fold (1.53-1.91). The AUC of the active metabolite fingolimod-phosphate was increased to a similar extent by 1.67-fold (1.50-1.85). Ketoconazole predose plasma levels were not altered by fingolimod. The magnitude of this interaction suggests that a proactive dose reduction of fingolimod is not necessary when adding ketoconazole to a fingolimod regimen. The clinician, however, should be aware of this interaction and bear in mind the possibility of a fingolimod dose reduction based on clinical monitoring.

Keywords: Immunomodulators; fingolimod; ketoconazole; drug interactions; CYP4F2

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Fingolimod is an orally administered sphingosine-1-phosphate receptor modulator in clinical development for the treatment of multiple sclerosis. Sphingosine-1-phosphate has 5 known receptors that are involved in multiple biological processes including leukocyte recirculation, neurogenesis, neural cell function, endothelial cell function, vasoregulation, and cardiovascular development.¹

Fingolimod exerts a beneficial effect in multiple sclerosis by retaining autoaggressive lymphocytes in the lymph nodes, away from the central nervous system where they are involved in inflammation and tissue damage.²

After oral administration, fingolimod is reversibly phosphorylated by sphingosine kinase to form the active moiety fingolimod-phosphate. In addition, fingolimod is irreversibly metabolized to a series of carboxylic acid metabolites that are subsequently excreted in the urine. The elimination half-life is 8.8 days, and the apparent clearance is 10.8 L/h.³ *In vitro* enzyme phenotyping experiments indicated that cytochrome CYP4F2 is the predominant isozyme contributing to fingolimod hydroxylation at the terminal methyl group of the octyl side chain, which is the first step of fingolimod oxidative

From Novartis Pharmaceuticals, Basel, Switzerland, and East Hanover, New Jersey (Dr Kovarik, Mr Dole, Dr Riviere, Dr Pommier, Mr Maton, Dr Jin, Dr Schmouder), and Clinical Pharmacology of Miami, Inc, Miami, Florida (Dr Lasseter). Submitted for publication August 28, 2008; revised version accepted October 30, 2008. Address for correspondence: John M. Kovarik, PhD, FCP, Novartis Pharma, Building WSJ 210.427, 4002 Basel, Switzerland.

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metabolism.⁴ In our standard workup to screen in vitro for potential drug interactions between a drug in development and comedications in clinical medicine, we found that ketoconazole, a well-known CYP3A4 strong inhibitor, significantly inhibited the oxidative metabolism of fingolimod by human liver microsomes and by recombinant CYP4F2. We were puzzled by these results since ketoconazole is generally thought to be a selective inhibitor of CYP3A4, and this isozyme does not play a significant role in the metabolism of fingolimod in vitro. We repeated the enzyme phenotyping experiment with ketoconazole along with the highly selective CYP3A inhibitor azamulin, which strongly inhibits CYP3A ($IC_{50} < 1 \mu M$) but weakly inhibits CYP4F2 ($IC_{50} = 46 \mu M$) in vitro.⁵ In the presence of 5 and 10 μM azamulin, the biotransformation rate of fingolimod was only slightly reduced by 9% to 25%. By contrast, ketoconazole at 4 to 10 μM reduced the fingolimod biotransformation rate by 67% to 88%.

The in vitro results with azamulin confirmed the minor role of CYP3A in the biotransformation of fingolimod and furthermore implied that ketoconazole may be an inhibitor of CYP4F2. The in vitro experiment, in which ketoconazole inhibited the biotransformation of fingolimod by recombinant human CYP4F2, strengthened the inference that ketoconazole can inhibit CYP4F2. We wanted to test the clinical relevance of CYP4F2 inhibition in a drug interaction study in compliance with standard regulatory guidance, which recommends that a strong inhibitor of the cytochrome pathway that predominates in the biotransformation of a drug in development be quantified in a clinical study.⁶ The CYP4F family primarily metabolizes endogenous substances such as fatty acids, eicosinoids, and leukotrienes⁷ but also xenobiotics such as the antiparasitic prodrug DB289.⁸ The literature is relatively silent on inhibitors of this isozyme inasmuch as we could not find any commonly used medication to serve as a probe inhibitor in our study. The in vitro inhibitory constant (K_i) for ketoconazole on fingolimod biotransformation was 0.74 μM in human liver microsomes, and therapeutic plasma levels of ketoconazole were 1 to 6 $\mu g/mL$ or 2 to 12 μM .⁹ Since the latter concentrations exceed the in vitro inhibitory concentration by 3- to 16-fold, a pharmacokinetic drug interaction of ketoconazole on fingolimod was considered likely, and we, therefore, used ketoconazole as our probe inhibitor of CYP4F2.

METHODS

Study Design

The protocol was reviewed and approved by the Independent Investigational Review Board, Inc (Miami, FL). The study was performed at the Clinical Pharmacology Research Unit of SFBC International. This was an open-label, 2-period, single-sequence, crossover study intended for 20 healthy subjects. In period 1 (days 1-35), subjects received a single 5-mg dose of fingolimod on day 1 with pharmacokinetic blood sampling and clinical assessments up to day 35. In period 2 (days 36-73), subjects received ketoconazole 200 mg twice daily for 9 days (days 36-44) and a single 5-mg dose of fingolimod coadministered on the 4th day of ketoconazole treatment (day 39). Pharmacokinetic blood sampling and clinical assessments were performed up to day 73. Because fingolimod is present systemically for a prolonged period postdose (1 month after 5 mg), we could not justify coadministering ketoconazole for this full time span. Instead, we coadministered ketoconazole for 5 days to cover fully fingolimod's absorption phase, reasoning that this would be sufficient to reveal a potential drug interaction.

We chose a single-sequence rather than a randomized 2-sequence study design because the effect of ketoconazole on fingolimod pharmacokinetics was not known, precluding our ability to determine the length of the washout needed between study periods to avoid fingolimod carryover if subjects received ketoconazole in period 1. The 5-mg dose of fingolimod was chosen because it allows full characterization of the fingolimod concentration-time curve and was the highest dose used in clinical development trials. The chosen ketoconazole regimen is 1 of the 2 regimens recommended by regulatory authorities for ketoconazole drug interaction studies.⁶

Based on coefficients of variation for fingolimod C_{max} (22%) and AUC (18%) from a previous clinical pharmacology study, we derived a sample size of 20 subjects. This would yield 80% power to demonstrate whether the 90% confidence interval around the geometric mean test/reference ratio of fingolimod C_{max} and AUC are contained in the standard bioequivalence range of 0.80 to 1.25.

Study Population and Disposition

Subjects granted written informed consent to participate in the study. We enrolled 28 subjects, consisting

of 16 men and 12 women aged 39.3 ± 9.8 years (range, 19-50 years) and weighing 70.6 ± 10.0 kg (range, 50-100 kg). Twelve subjects were white, 10 were black, and 6 were of other ethnicities. Six subjects did not complete the study: 3 subjects withdrew consent, 2 subjects were lost to follow-up due to the prolonged study duration, and 1 subject was withdrawn from the study for violating the protocol by not disclosing that he had hypertension and was taking enalapril. Consequently, 22 subjects completed the study.

Domiciling and Drug Administration

Subjects were housed at the clinical site for the first 5 days of each study period; hence, from days 1 to 5 and 39 to 43. They returned to the site for clinical and pharmacokinetic assessments on days 14, 21, 28, and 35 in period 1 and days 52, 59, 66, and 73 in period 2 to characterize the terminal phase of the fingolimod concentration-time profiles. We supplied fingolimod capsules of 2.5-mg dose strength, and the study site purchased ketoconazole 200-mg tablets (Teva Pharmaceuticals, Tikva, Israel). A single 5-mg dose of fingolimod was administered on days 1 and 39. Ketoconazole 200-mg doses were administered twice daily on days 36 through 44. Study medications were administered with 240 mL water by the study center personnel. Subjects fasted for 10 hours before morning administrations of fingolimod and ketoconazole and for 2 hours before to 1 hour after evening administrations of ketoconazole. Meals were standardized during the in-house parts of the study.

Clinical Assessments and Heart Rate Evaluation

Standard biochemistry, hematology, and urinalysis laboratory parameters and 12-lead electrocardiography were performed at baseline before each period and at the end of the study. Because fingolimod has a mild, reversible negative chronotropic effect on heart rate,¹⁰ we monitored vital signs (pulse and blood pressure) frequently on both days of fingolimod administration predose and then 1, 2, 3, 4, 6, 8, and 12 hours postdose. Vital signs were also recorded in the morning of all other in-house study days and at each outpatient clinical visit. Heart rate data were graphed with respect to time postdose and inspected for temporal trends. The heart rate-time course was characterized by the predose rate, the nadir rate and its time of occurrence, and the area under the effect-time curve ($AUEC_{(0-12)}$) over the 12-hour monitoring period.

Pharmacokinetic Assessments and Bioanalytics

Blood samples for the determination of fingolimod and fingolimod-phosphate were collected predose and then 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 312, 480, 648, and 816 hours postdose in each study period. For ketoconazole, venous blood samples were collected before the morning dose on days 38, 39, 40, 42, and 44.

Blood concentrations of fingolimod and fingolimod-phosphate were determined separately by validated liquid chromatography methods and tandem mass spectrometry as previously described.¹¹ As applied in this study for fingolimod, there were 7 calibration concentrations (range, 0.08-30 ng/mL) and 4 quality control concentrations (0.24, 2, 5, 25 ng/mL). Quality control accuracy ranged from 96.7% to 102.8%, and precision ranged from -3.3% to 2.8%. The lower quantification limit was 0.08 ng/mL. For fingolimod-phosphate, there were 7 calibration concentrations (range, 1-50 ng/mL) and 3 quality control concentrations (2, 7.5, 40 ng/mL). Quality control accuracy ranged from 96.0% to 103.7%, and precision ranged from -4.0% to 3.7%. The lower quantification limit was 1 ng/mL. Ketoconazole plasma concentrations were determined by high-performance liquid chromatography with ultraviolet detection. There were 7 calibration concentrations (range, 0.01-5 μ g/mL) and 3 quality control concentrations (0.02, 2.5, 4 μ g/mL). Quality control accuracy ranged from 103.2% to 109.6%, and precision ranged from -3.3% to 8.0%. The lower quantification limit was 0.01 μ g/mL.

For fingolimod, standard noncompartmental pharmacokinetic parameters included the lag time postdose until blood concentrations were quantifiable (t_{lag}), the time postdose when the maximum concentration occurred (t_{max}), the maximum concentration (C_{max}), the area under the concentration-time curve by trapezoidal summation over the 120 hours during which ketoconazole was coadministered ($AUC_{(0-120h)}$), the AUC extrapolated to infinity (AUC), and the terminal half-life by unweighted log-linear regression ($t_{1/2}$). Given the lower blood levels of fingolimod-phosphate and the higher assay quantification limit, the terminal half-life could not be estimated nor could the AUC be extrapolated to infinity.

Statistical Evaluation

Fingolimod pharmacokinetic parameters were log-transformed and compared between treatments using a linear mixed-effects model with treatment as a fixed factor and subject as a random factor.

Table I Fingolimod Pharmacokinetics

Parameter	Fingolimod Alone	Fingolimod With Ketoconazole	Ratio of Geometric Means (90% CI)
Fingolimod			
t_{lag} , h	0.25 (0.25–0.5)	0.25 (0–0.25)	—
t_{max} , h	12 (8–36)	12 (3–48)	—
C_{max} , ng/mL	3.9 ± 0.7	4.8 ± 1.1	1.22 (1.15–1.30)
$AUC_{(0-120h)}$, ng·h/mL	312 ± 67	439 ± 98	1.40 (1.31–1.50)
AUC, ng·h/mL	665 ± 202	1124 ± 293	1.71 (1.53–1.91)
$t_{1/2}$, d	5.1 ± 1.6	5.8 ± 1.6	1.15 (1.06–1.26)
Fingolimod-phosphate			
t_{lag} , h	2 (1–4)	2 (1.5–4)	—
t_{max} , h	8 (6–12)	8 (6–12)	—
C_{max} , ng/mL	4.5 ± 1.3	4.4 ± 1.1	0.99 (0.92–1.06)
$AUC_{(0-120h)}$, ng·h/mL	128 ± 49	217 ± 99	1.67 (1.50–1.85)

Values are mean ± SD, except for temporal parameters, which are median (range). t_{lag} , lag-time postdose until blood levels are quantifiable; t_{max} , time postdose when C_{max} occurs; C_{max} , maximum concentration; $AUC_{(0-120h)}$, area under the concentration-time curve to 120 hours postdose corresponding to the 5-day interval over which ketoconazole was coadministered; AUC, AUC extrapolated to infinity.

Differences in least squares means were calculated along with 90% confidence intervals. These were back-transformed onto the original scale to give test/reference ratios of the parameter geometric means and their 90% confidence intervals. Steady-state ketoconazole predose concentrations in the absence of fingolimod and in its presence were compared using a repeated-measures mixed linear model fitting subject, treatment, and study day as model factors.

RESULTS

Pharmacokinetics of Fingolimod

Table I summarizes the pharmacokinetic parameters and statistical comparisons. Figures 1 and 2 show the mean concentration-time profiles. When administered alone, fingolimod was quantifiable in blood either without or with a slight lag time of up to 0.5 hours postdose. No influence of ketoconazole on mean fingolimod concentrations in the first hour postdose was evident, as seen in Figure 1. From 1.5 to 12 hours postdose, fingolimod mean concentrations increased to higher levels in the presence of ketoconazole compared with its absence. Ketoconazole did not affect the time to reach the peak concentration (t_{max}) and did not alter C_{max} in most subjects. Specifically, 13 subjects (59%) had no change in C_{max} (test/reference ratios of 0.84 to 1.25), and 9 subjects (41%) had increases (ratios of 1.27 to 1.62). Across the full study population, there was a weak average

increase in C_{max} of 1.22-fold. Intersubject variability in C_{max} was not altered by ketoconazole: 18% alone versus 23% with ketoconazole.

Ketoconazole had a minor influence on fingolimod-phosphate mean concentrations in the first 12 hours postdose. The initial lag time of 1 to 4 hours for this analyte likely reflects the higher assay quantification limit rather than delayed formation. When fingolimod was given alone, the time to reach the peak occurred earlier for fingolimod-phosphate (median 8 hours) versus fingolimod (median 12 hours), and the C_{max} of fingolimod-phosphate was higher than that of fingolimod. Ketoconazole coadministration did not alter fingolimod-phosphate t_{max} or C_{max} .

Figure 2 shows that the concentration profile of fingolimod was elevated in the presence of ketoconazole but declined in parallel with that from monotherapy in the terminal phase. Most subjects had an increase in $AUC_{(0-120h)}$ in the presence of ketoconazole. Specifically, $AUC_{(0-120h)}$ was not altered to a clinically relevant extent in 8 subjects (ratios of 1.06 to 1.24) and was weakly increased in the remaining 14 subjects (ratios of 1.27 to 1.85). Over the full study population, $AUC_{(0-120h)}$ increased 1.40-fold. Intersubject variability for $AUC_{(0-120h)}$ was similar under both treatment conditions: 22% alone versus 22% with ketoconazole. For the full AUC extrapolated to infinity, exposure was not altered in 3 subjects (ratios of 0.81, 1.10, and 1.22), was increased weakly in 14 subjects (ratios of 1.32 to 1.96), and was increased moderately in 5 subjects

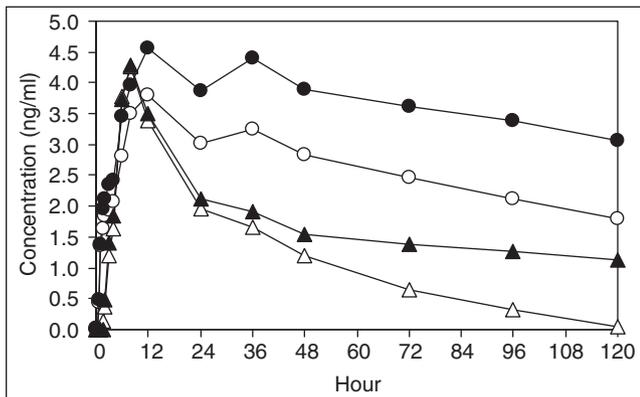


Figure 1. Mean concentration-time profiles over the 5-day period of ketoconazole coadministration. Designated are fingolimod alone (open circles) and with ketoconazole (filled circles) and fingolimod-phosphate alone (open triangles) and with ketoconazole (filled triangles).

(ratios of 2.29 to 2.86). Over the full study population, AUC increased 1.71-fold. Ketoconazole coadministration did not appear to alter the decline in fingolimod blood concentrations during the 5 days of coadministration nor after stopping ketoconazole, as illustrated in Figures 1 and 2.

Between days 2 and 5 postdose, mean concentrations of fingolimod-phosphate appeared to decline more rapidly after monotherapy than in the presence of ketoconazole, as shown in Figure 1. This was due in part to the earlier dropping of concentrations below the assay quantification limit after monotherapy, whereby unquantifiable levels were set to 0 ng/mL and weighed the overall mean values at terminal time points downward. After coadministration with ketoconazole, fingolimod-phosphate concentrations were elevated and remained above the assay quantification limit for a longer time postdose, avoiding a biased mean concentration-time slope. The $AUC_{(0-120h)}$ test/reference ratios ranged from 0.91 to 2.84 across the population, with an average 1.67-fold increase of $AUC_{(0-120h)}$ in the presence of ketoconazole.

Ketoconazole Predose Concentrations

Mean predose ketoconazole concentrations reached steady state by the 4th day of twice-daily administration, with a value of 1.6 ± 1.0 $\mu\text{g/mL}$ on day 38 and 2.0 ± 1.4 $\mu\text{g/mL}$ on day 39 just before the dose of fingolimod. Coadministration of fingolimod did not alter ketoconazole trough levels, which were 2.0 ± 1.2 $\mu\text{g/mL}$ on day 40, 2.2 ± 1.4 $\mu\text{g/mL}$ on day 42, and 2.0 ± 1.3 $\mu\text{g/mL}$ on day 44. Statistical comparison of

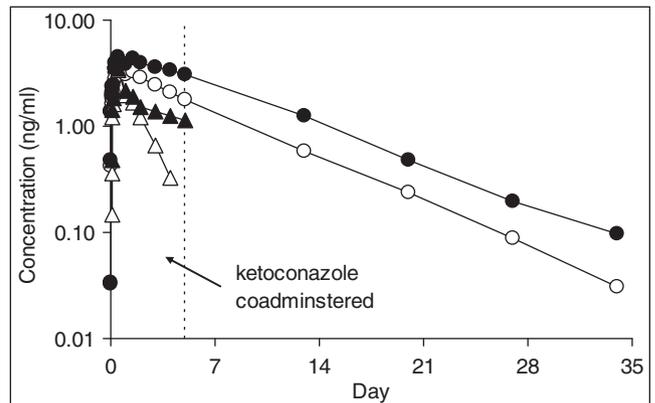


Figure 2. The same data as in Figure 1 but with concentrations on a logarithmic scale plotted over the full 35-day pharmacokinetic blood sample collection period. Ketoconazole was coadministered to day 5.

the values on day 39 to those on days 40 to 44 confirmed lack of an effect of fingolimod on ketoconazole ($P \geq .17$).

Exposure-Response Associations

Graphical exploration and regression analysis did not reveal any association between the ketoconazole trough level before the dose of fingolimod was coadministered versus the fold increase in fingolimod C_{max} or AUC. On the other hand, as shown in Figure 3, there was a curvilinear relationship between baseline fingolimod AUC on monotherapy and the fold increase in AUC in the presence of ketoconazole. Subjects with lower fingolimod exposure during monotherapy tended to have the highest increases in exposure when ketoconazole was coadministered.

Clinical Observations and Heart Rate Responses

There were 18 adverse events considered by the investigator to be drug related: 10 events of headache (attributed to fingolimod alone, ketoconazole alone, and both drugs combined), 4 events of dizziness (fingolimod alone and ketoconazole alone), 1 event each of constipation and nausea (both ketoconazole alone), and 1 event each of visual disturbance and rash (fingolimod alone). All adverse event resolved by the end of the study.

There were no clinically relevant changes in laboratory parameters, with the exception of low lymphocyte or white blood cell counts in 7 subjects. This is an expected effect of fingolimod as one of its pharmacological actions is to retain a subset of lymphocytes in

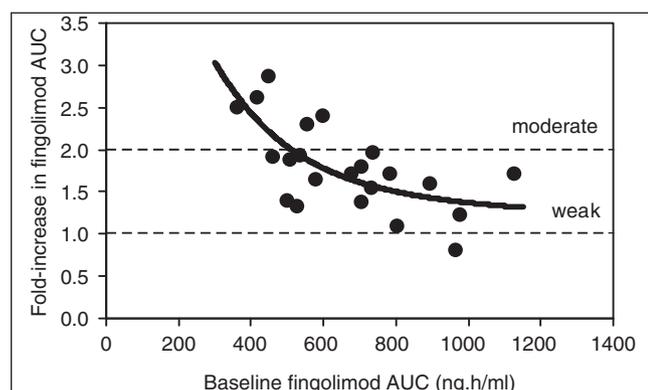


Figure 3. Scatterplot of baseline fingolimod AUC and the fold increase in AUC in the presence of ketoconazole. Shown is a trendline based on an inhibitory I_{max} model and categorical bounds for weak (<2-fold) and moderate (≥ 2 -fold) interactions.

the lymph nodes, thereby reducing the peripheral blood lymphocyte count. This is a reversible effect, and lymphocyte counts recovered over the study course back to baseline without intervention.

There were no clinically relevant changes in electrocardiograms or vital signs with the exception of decreased heart rate, which is an expected pharmacological effect of fingolimod via binding at sphingosine-1-phosphate receptors on sinoatrial node cells. As summarized in Table II, heart rate decreased acutely by about 25% after drug administration, reaching a nadir by 3 to 4 hours postdose. Neither the nadir nor the area under the heart rate–time curve differed between treatments. The morning heart rate recovered back to baseline by 48 hours postdose without clinical intervention.

DISCUSSION

We conducted this clinical drug interaction study to determine if a CYP4F2 inhibitor alters the pharmacokinetics of fingolimod, which is predominantly metabolized via this enzyme. If an alteration were observed, the intention was to quantify this effect to serve as a general indication as to whether fingolimod is sensitive to CYP4F2 inhibition to a clinically relevant extent and, more concretely, to yield recommendations for clinicians if ketoconazole needs to be added to a fingolimod regimen.

Overall, the influence of ketoconazole on fingolimod was a weak interaction with a 1.7-fold increase in fingolimod and fingolimod-phosphate AUCs. These in vivo data are in agreement with in vitro results from human liver microsome experiments, in which

Table II Heart Rate Responses

Response	Fingolimod Alone	Fingolimod With Ketoconazole
Predose rate, bpm	68 ± 9	66 ± 8
Time to nadir, h	3 (1-8)	4 (2-12)
Nadir rate, bpm	50 ± 6	52 ± 6
Nadir rate, % of predose	74 ± 10	79 ± 8
AUE _(0-12h) , bpm × h	703 ± 69	723 ± 79
Rate at 24 h, bpm	60 ± 8	60 ± 8
Rate at 48 h, bpm	67 ± 9	63 ± 7
Rate at 72 h, bpm	65 ± 6	63 ± 7

Data are mean ± SD, except for time to nadir, which is median (range). AUE, area under the effect-time curve.

ketoconazole at 4 to 10 μ M reduced the fingolimod biotransformation rate by 67% to 88%. While most subjects had a weak interaction (AUC fold increase <2), a few had a moderate interaction (≥ 2 -fold increase). In this context, we noted that subjects with low fingolimod AUC at baseline (and presumably higher CYP4F2 activity) tended to be more susceptible to an inhibition interaction by ketoconazole and exhibited higher magnitudes of increase in fingolimod AUC, as shown in Figure 3. However, the magnitude of the interaction did not exceed a 3-fold increase in fingolimod or fingolimod-phosphate exposure in any subject. Furthermore, the increased exposure to fingolimod-phosphate in the presence of ketoconazole did not augment fingolimod’s negative chronotropic effect, as summarized in Table II.

Our study design and interpretation of the results have some limitations. We cannot rule out that a stronger interaction on fingolimod might have occurred if ketoconazole had been continuously coadministration throughout the full 35-day period of fingolimod pharmacokinetic blood sampling. Understandably, we could not justify coadministration of ketoconazole for such a prolonged time in healthy subjects. At a minimum, the 5-day period of coadministration covered the full absorption and a major portion of the distribution phases of fingolimod.

Second, while we attribute the effect of ketoconazole on fingolimod primarily to inhibition of CYP4F2, we acknowledge that this may not be the sole mechanism. Other enzymes and transporters also play minor roles in fingolimod biotransformation in vitro so that inhibition of these pathways by ketoconazole may have contributed to the increase in fingolimod exposure, but we believe these contributions to be negligible. For example, ketoconazole is a strong inhibitor of CYP3A4. However, using enzyme kinetic data with recombinant human CYP

isoenzymes, the fraction of fingolimod metabolized by CYP3A4 was negligible (1.6%, unpublished data). Therefore, specific CYP3A4 inhibitors are not expected to have similar effects on fingolimod exposure as observed for ketoconazole. Ketoconazole is also an inhibitor of MDR1. It is not known if fingolimod is a substrate of this transporter *in vitro*; however, when the strong MDR1 inhibitor cyclosporin was coadministered with fingolimod in healthy subjects, fingolimod pharmacokinetics were not altered.¹² Hence, CYP3A4 and MDR1 inhibition by ketoconazole are unlikely to have played a clinically relevant role in this drug interaction on fingolimod.

Finally, it is clinically desirable to quantify the maximum effect a CYP4F2 inhibitor would have on fingolimod in order to put potential drug interactions via this pathway into perspective and to inform clinicians about what to expect if they coadminister a medication that inhibits CYP4F2. However, in the absence of additional drug interaction studies with CYP4F2 inhibitors, this is not possible, nor is it possible to rank fingolimod with regard to its sensitivity to CYP4F2 inhibition based on this single clinical study.

We conclude from this study that coadministration of a single 5-mg dose of fingolimod with steady-state ketoconazole weakly increased fingolimod and fingolimod-phosphate exposure on average by 1.7-fold. The magnitude of this interaction suggests that a proactive dose reduction of fingolimod is not necessary when adding ketoconazole to a fingolimod regimen. The clinician, however, should be aware of this interaction and bear in mind the possibility of a fingolimod dose reduction based on clinical monitoring.

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