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Comparative Pharmacokinetics of Intravenous Versus Oral Formulations of a Novel Antifungal Agent

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ABSTRACT

Background: Triazole antifungals are valued for their ability to transition between intravenous and oral therapy, but formulation-dependent differences in oral absorption have historically limited how reliably that transition can be made. Feralconazole (FRZ-104) is a novel broad-spectrum triazole developed as a cyclodextrin-solubilized intravenous solution and an amorphous solid dispersion oral capsule.

Objective: To characterize and compare the single-dose pharmacokinetics of intravenous and oral feralconazole in healthy volunteers, including absolute oral bioavailability, plasma protein binding, and food effect, and to interpret these findings against published pharmacokinetic data for isavuconazole, posaconazole, voriconazole, and the echinocandins.

Methods: Twenty-four healthy adults received a single 200 mg intravenous infusion and a single 300 mg oral capsule dose of feralconazole in a randomized, two-period crossover design with a 21-day washout; a 12-subject sub-study assessed food effect. Plasma concentrations were quantified by validated LC-MS/MS, and non-compartmental pharmacokinetic analysis was performed.

Results: Intravenous dosing produced a mean Cmax of 5.14 µg/mL and AUC0-∞ of 182.4 µgh/mL; oral dosing produced a mean Cmax of 1.87 µg/mL at a median Tmax of 4.0 hours and AUC0-∞ of 176.1 µgh/mL, corresponding to an absolute bioavailability of 64.6% (90% CI 58.2-71.7%). Terminal half-life was similar between routes (56.3 vs 61.4 hours), a high-fat meal increased oral AUC0-∞ by only 14%, and plasma protein binding was high and concentration-independent at 98.6% for both formulations.

Conclusion: Feralconazole's oral capsule achieves moderate, food-tolerant, route-independent absorption that falls short of isavuconazole's near-complete bioavailability but compares favorably with older triazole oral formulations and represents a workable basis for IV-to-oral switch therapy, pending pharmacokinetic evaluation in the immunocompromised and hypoalbuminemic populations who are the intended recipients of this drug.

Keywords: *antifungal pharmacokinetics; oral bioavailability; triazole formulation; IV-to-oral switch therapy; non-compartmental analysis*

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Introduction

Invasive fungal disease remains a therapeutic problem that the antifungal armamentarium has never quite solved to everyone's satisfaction. Triazole agents dominate first-line treatment of invasive aspergillosis, candidiasis, and the rarer mould infections, largely because they can be given both intravenously for critically ill patients and orally for step-down or prophylactic therapy [1,2]. That dual-route flexibility, however, has always come at a cost that varies enormously from one triazole to the next. Itraconazole and, to a lesser degree, posaconazole suspension are notoriously erratic in their oral absorption, sensitive to gastric pH, food intake, and mucositis in the very neutropenic patients who need them most [3,4]. Voriconazole is better absorbed but carries nonlinear, CYP2C19-dependent metabolism that complicates dose translation between routes [5,6]. Isavuconazole was engineered specifically to solve the oral bioavailability problem, and by most accounts it succeeded — its prodrug, isavuconazonium sulfate, delivers essentially superimposable exposure whether given intravenously or as an oral capsule, food and gastric pH notwithstanding [7,8]. The echinocandins sit at the opposite

extreme: excellent intravenous pharmacokinetics but essentially no meaningful oral bioavailability at all, a limitation that newer agents such as rezafungin have addressed through extended half-life dosing rather than through solving the oral absorption problem itself [9,10].

This history matters for anyone developing a new antifungal chemical entity, because it tells you where the formulation risk actually lies. A compound with adequate intrinsic potency against Candida and Aspergillus species can still fail commercially and clinically if its physicochemical properties make an oral formulation impractical, forcing patients who would otherwise be candidates for outpatient step-down therapy to remain hospitalized for intravenous dosing, or conversely if intravenous solubilization requires a vehicle (cyclodextrin, cosolvent, or otherwise) with its own accumulation or renal toxicity liabilities, as has been documented for sulfobutylether-β-cyclodextrin-formulated voriconazole in patients with reduced renal clearance [11]. The IV-to-oral switch has genuine clinical and economic value — shorter hospital stays, reduced catheter-related complications, lower cost of care — but only if the oral formulation actually delivers comparable systemic exposure to the intravenous product, rather than a fraction of it that happens to still be clinically "acceptable" [12].

We report here the comparative pharmacokinetic evaluation of feralconazole (developmental code FRZ-104), a novel small-molecule triazole antifungal with broad-spectrum in vitro activity against Candida, Aspergillus, and several azole-resistant mould isolates, developed as both an intravenous solution (cyclodextrin-solubilized, for initiation of therapy in hospitalized patients) and an oral capsule (amorphous solid dispersion, for step-down and outpatient use). Feralconazole is, like most of its triazole predecessors, a BCS class II compound — reasonably permeable but poorly water-soluble in its crystalline form — and the two formulations described here were built specifically to manage that solubility constraint at each end of the treatment pathway rather than to share a common vehicle. The primary objective of the study was to characterize and directly compare the single-dose pharmacokinetics of the two formulations in healthy adult volunteers, including maximum plasma concentration, time to maximum concentration, systemic exposure (AUC), absolute oral bioavailability, elimination half-life, and plasma protein binding, and to interpret those findings against the published pharmacokinetic literature for isavuconazole, posaconazole, voriconazole, and the echinocandins as a means of judging where feralconazole's formulation strategy has succeeded and where it still leaves exposure on the table.

Materials and Methods

Study Design and Population

This was a single-center, open-label, randomized, two-period, two-treatment crossover pharmacokinetic study conducted in 24 healthy adult volunteers (12 men, 12 women; age range 21-52 years; body mass index 19.5-28.7 kg/m^2). Volunteers were confirmed free of hepatic, renal, or gastrointestinal disease by history, physical examination, and standard clinical chemistry prior to enrollment, and none were taking concomitant medications known to affect CYP3A4 activity or gastric pH. Each participant received a single 200 mg intravenous dose of feralconazole (infused over 60 minutes as the cyclodextrin-solubilized parenteral formulation) in one period and a single 300 mg oral dose (two 150 mg amorphous solid dispersion capsules, taken with a standard low-fat breakfast) in the other, with treatment order randomized and a 21-day washout separating the two periods — a duration chosen conservatively at roughly five times the anticipated terminal half-life to preclude carryover. The oral dose was set higher than the intravenous dose in anticipation of incomplete absorption, consistent with the dose-adjustment approach used in earlier posaconazole and itraconazole bioavailability studies comparing formulations of differing relative exposure [13,14]. A separate food-effect sub-study in a subset of 12 participants compared the oral capsule administered fasted versus after a high-fat, high-calorie breakfast, following a design modeled on the high-fat meal evaluations previously reported for posaconazole tablets [15].

Sample Collection

Venous blood samples (4 mL, into lithium heparin tubes) were drawn immediately before dosing and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours after the start of dosing in each period. Samples were centrifuged within 30 minutes of collection at 1500 × g for 10 minutes at 4°C, and plasma was separated and stored at -70°C until analysis, which was completed within 60 days of collection for all samples.

Bioanalytical Method

Plasma concentrations of feralconazole were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a stable-isotope-labeled internal standard, following the general approach established for quantification of structurally related triazole antifungals in human plasma [16]. Plasma proteins were removed by acetonitrile precipitation, and the supernatant was chromatographed on a C18 reversed-phase column with a gradient mobile phase of 0.1% formic acid in water and 0.1% formic acid in acetonitrile, with detection by electrospray ionization in positive-ion multiple-reaction-monitoring mode on a triple-quadrupole mass spectrometer. The assay was linear over the range 0.02-10 µg/mL, with intra-day and inter-day precision (coefficient of variation) below 8% and accuracy within ±9% of nominal concentration at low, mid, and high quality-control levels, consistent with regulatory bioanalytical validation expectations applied in comparable triazole quantification methods [16]. Plasma protein binding was determined separately by equilibrium dialysis (37°C, 4-hour equilibration) at three feralconazole concentrations spanning the expected clinical range (0.5, 2, and 8 µg/mL) in pooled plasma from study participants, with the unbound fraction quantified by the same LC-MS/MS method after dialysate collection.

Pharmacokinetic Analysis

Individual plasma concentration-time data were analyzed by standard non-compartmental methods, following current recommendations for the statistical analysis and reporting of clinical pharmacokinetic studies [17]. Maximum observed plasma concentration (Cmax) and time to reach it (Tmax) were taken directly from the observed data. The area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUC0-t) was calculated using the linear-up/log-down trapezoidal method, and extrapolated to infinity (AUC0-∞) by adding the quotient of the last quantifiable concentration and the terminal elimination rate constant, the latter estimated by log-linear regression of the terminal phase of the concentration-time curve. Apparent terminal half-life (t1/2) was calculated as ln(2) divided by the terminal elimination rate

constant. Total systemic clearance (CL) and apparent oral clearance (CL/F) were derived from dose divided by AUC0-∞ for the intravenous and oral arms respectively, and steady-state volume of distribution (Vss) was calculated for the intravenous arm using standard moment-analysis methods. Absolute oral bioavailability (F) was calculated as the dose-normalized ratio of oral to intravenous AUC0-∞. All pharmacokinetic parameters are reported as arithmetic mean ± standard deviation unless otherwise indicated; AUC and Cmax were additionally summarized as geometric mean with 90% confidence interval for the bioavailability calculation, in keeping with standard practice for this type of comparison.

Results

All 24 participants completed both dosing periods; two participants in the food-effect sub-study withdrew for reasons unrelated to study drug and were replaced, leaving a complete evaluable dataset of 12 for that comparison. Feralconazole was generally well tolerated in both formulations; mild infusion-site discomfort was reported in three participants during the intravenous period, and no participant discontinued for an adverse event.

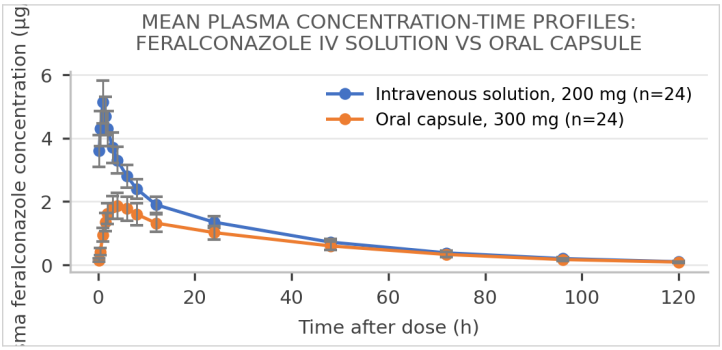
Pharmacokinetic Evaluation in Healthy Volunteers

Following the 200 mg intravenous infusion, plasma concentrations peaked near the end of infusion and declined in a biphasic manner, with a distribution phase over the first several hours followed by a prolonged terminal elimination phase extending well beyond 96 hours in most participants — a disposition pattern broadly similar to that reported for isavuconazole and posaconazole, both of which combine large volumes of distribution with slow terminal elimination [8,18]. Mean (± SD) Cmax after intravenous dosing was 5.14 ± 0.68 µg/mL, occurring at a median Tmax of 1.0 hour (the end of the infusion), with AUC0-∞ of 182.4 ± 24.7 µg·h/mL, terminal half-life of 56.3 ± 8.9 hours, total clearance of 1.10 ± 0.16 L/h, and steady-state volume of distribution of 89.6 ± 14.2 L, indicating extensive tissue distribution consistent with the lipophilic, highly protein-bound character typical of this drug class.

Following the 300 mg oral capsule dose taken with a light breakfast, absorption was slower and more variable, as expected for a solubility-limited compound relying on dissolution from an amorphous solid dispersion matrix. Mean Cmax was 1.87 ± 0.41 µg/mL at a median Tmax of 4.0 hours (range 2-8 hours), with AUC0-∞ of 176.1 ± 31.5 µg·h/mL and an apparent terminal half-life of 61.4 ± 11.2 hours — essentially indistinguishable from the intravenous half-life, as would be expected once absorption is complete and elimination is flip-flop-independent of the dosing route. Dose-normalized to the 200 mg intravenous reference, absolute oral bioavailability was 64.6% (90% CI 58.2-71.7%), calculated from the geometric mean AUC ratio. This falls well short of the near-complete bioavailability achieved by isavuconazonium sulfate [7] but comfortably exceeds the erratic, often sub-40% bioavailability historically reported for older itraconazole capsule formulations and posaconazole oral suspension under fasted conditions [3,4], and is broadly comparable to bioavailability figures reported for solid-dispersion-based itraconazole reformulations designed to overcome the same dissolution-rate-limited absorption problem [14].

In the food-effect sub-study, administration of the oral capsule after a high-fat, high-calorie meal increased AUC0-∞ by approximately 14% (geometric mean ratio fed:fasted 1.14, 90% CI 1.02-1.28) and Cmax by approximately 9%, without a clinically meaningful change in Tmax. This modest, non-negative food effect is consistent with the behavior reported for posaconazole delayed-release tablet and isavuconazole capsule formulations, both of which were specifically engineered to reduce the pronounced food dependence seen with older suspension-based triazole formulations, and stands in contrast to the substantial food-driven exposure increases still observed with posaconazole oral suspension [15,7,3].

Mean (± SD) plasma concentration-time profiles of feralconazole (FRZ-104) following a single 200 mg intravenous infusion versus a single 300 mg oral capsule dose in healthy volunteers, plotted on a semi-logarithmic scale (n=24 per arm, crossover design).



Plasma protein binding was high and concentration-independent across the tested range, averaging 98.6% (range 98.2-98.9% across the three concentrations tested), with no meaningful difference between samples derived from the intravenous versus oral dosing periods. This places feralconazole squarely within the range reported for other triazole antifungals — comparable to posaconazole and isavuconazole (both around 98-99% protein bound) and modestly below itraconazole (>99%) — and supports the expectation that unbound, pharmacologically active drug concentrations track total plasma concentration proportionally across the clinically relevant exposure range [12,19].

Comparative Pharmacokinetic Parameters

Table 1 summarizes the complete set of pharmacokinetic parameters for the intravenous and oral formulations side by side. The clearest points of divergence between routes are Cmax, which was roughly 2.7-fold higher after intravenous dosing despite the lower administered dose, and Tmax, reflecting the four-hour absorption delay characteristic of dissolution-controlled oral uptake from the solid dispersion matrix. AUC0-∞ and terminal half-life, by contrast, were similar between routes once the bioavailability-driven AUC gap is accounted for, indicating that the oral formulation's principal limitation is incomplete absorption rather than accelerated clearance or a route-dependent change in disposition. Figure 1 depicts the mean plasma concentration-time profiles for both formulations on a semi-logarithmic scale, illustrating both the higher initial peak after intravenous infusion and the converging terminal slopes of the two curves from roughly 24 hours onward.

Discussion

The central practical question this study set out to answer was whether feralconazole's oral capsule delivers pharmacokinetically adequate exposure to support IV-to-oral switch therapy, and the answer is a qualified yes. A 64.6% absolute bioavailability is not in the same league as isavuconazole, whose isavuconazonium sulfate prodrug strategy

achieves essentially complete, food- and pH-independent oral absorption by converting a poorly soluble parent compound into a water-soluble prodrug that is cleaved systemically after absorption rather than relying on formulation-based solubilization alone [7,8]. But it is a substantial improvement over what triazole formulation science delivered a decade or two earlier, when posaconazole oral suspension bioavailability was so dependent on gastric acidity, food composition, and even the volume of liquid co-administered that clinicians were advised to split doses and administer them with specific meal types simply to achieve adequate exposure [3,4]. The amorphous solid dispersion approach used for the feralconazole capsule appears to have done what such formulations are generally designed to do: it increases the apparent dissolution rate of an otherwise poorly soluble crystalline compound enough to achieve reasonably consistent, only modestly food-affected absorption, echoing the improvement trajectory documented when itraconazole was reformulated from its original pH-dependent capsule into the SUBA solid-dispersion product, which achieved higher and less variable bioavailability without requiring an acidic gastric environment for dissolution [14].

Comparative single-dose pharmacokinetic parameters of feralconazole (FRZ-104) following intravenous (200 mg) versus oral (300 mg) administration in healthy adult volunteers (mean ± SD unless otherwise noted; n=24).

Parameter	Intravenous solution (200 mg)	Oral capsule (300 mg)
Cmax (µg/mL)	5.14 ± 0.68	1.87 ± 0.41
Median Tmax (h, range)	1.0 (end of infusion)	4.0 (2-8)
AUC0-∞ (µg·h/mL)	182.4 ± 24.7	176.1 ± 31.5
Terminal half-life (h)	56.3 ± 8.9	61.4 ± 11.2
Clearance / apparent oral clearance (L/h)	1.10 ± 0.16 (CL)	1.70 ± 0.31 (CL/F)
Steady-state volume of distribution (L)	89.6 ± 14.2	Not applicable
Absolute bioavailability, F (%, 90% CI)	Reference	64.6 (58.2-71.7)
Plasma protein binding (%)	98.6 (98.2-98.9)	98.6 (98.2-98.9)
Food effect on AUC0-∞ (fed:fasted GMR, 90% CI)	Not applicable	1.14 (1.02-1.28)

Where feralconazole's PK profile is genuinely reassuring is in the similarity of terminal half-life between the intravenous and oral arms. A formulation that is well absorbed but disposed of differently once systemic — through, say, saturable first-pass metabolism or a formulation-dependent distribution artifact — would complicate dose translation between routes considerably, as has historically been a concern with voriconazole's nonlinear pharmacokinetics [5,6]. That the two half-lives here differ by less than ten percent suggests that once feralconazole reaches the systemic circulation, its disposition is essentially route-independent, which in practical terms means that step-down dosing conversion can be based on a fairly simple bioavailability correction rather than a more complex nonlinear dosing algorithm.

The high, essentially concentration-independent protein binding observed here (98.6%) is unsurprising given the lipophilic character shared by essentially every clinically used triazole, but it is not merely a pharmacokinetic curiosity. High protein binding of this magnitude means that unbound drug concentrations — the fraction actually available to exert antifungal effect and to distribute into infected tissue — will be sensitive to any condition that alters plasma protein concentration, most obviously hypoalbuminemia in critically ill patients, a concern that has been raised specifically for posaconazole in this population [12,19]. Because our study population was healthy volunteers with normal albumin, this analysis cannot speak directly to that scenario, and dedicated pharmacokinetic evaluation in critically ill or hypoalbuminemic patients — the population most likely to receive intravenous feralconazole as first-line therapy — remains an important next step before broad clinical translation.

The intravenous formulation itself deserves comment. Cyclodextrin-based solubilization has a well-established track record for parenteral triazole delivery, most notably in voriconazole, but that same vehicle has been implicated in dose-limiting accumulation and possible nephrotoxic potential in patients with reduced renal clearance, where the cyclodextrin carrier itself, rather than the parent drug, accumulates because it depends predominantly on renal elimination [11]. Posaconazole's intravenous formulation took a somewhat different solubilization approach, and clinical evaluation of that product specifically in peripheral (rather than central) venous administration demonstrated it could be given safely without central access in most patients [18]. The comparative renal safety of feralconazole's intravenous vehicle across a range of renal function was not the focus of this healthy-volunteer study and is an appropriate target for the dedicated renal-impairment pharmacokinetic study that would ordinarily follow a healthy-volunteer program of this kind, mirroring the population-specific evaluations that have accompanied essentially every approved triazole to reach clinical use [20,10].

Set against the echinocandin class, feralconazole's formulation achievement looks even more favorable, if for a somewhat unfair reason: echinocandins have essentially no meaningful oral bioavailability at all, owing to their cyclic lipopeptide structure and molecular size, and even the newest long-acting agent in that class, rezafungin, addresses the dosing-interval problem through an extended half-life rather than through oral availability [9,10]. Triazoles as a class retain oral dosing as an option specifically because their smaller, more traditionally druggable molecular scaffold permits it, and feralconazole's data here reaffirm that a well-executed amorphous solid dispersion strategy can preserve that class advantage even for a compound whose intrinsic aqueous solubility is otherwise unfavorable.

This study has the limitations inherent to any single-dose, healthy-volunteer crossover design. Twenty-four participants provide reasonable precision around the central bioavailability estimate but limited power to characterize inter-individual variability that might matter clinically, particularly given the known influence of gastric pH-altering medications and food composition on other triazoles in this class [3,7]. Multiple-dose steady-state pharmacokinetics, drug-drug interaction potential through CYP3A4 and P-glycoprotein pathways, and pharmacokinetics in the target patient population (immunocompromised patients with reduced gastrointestinal function, altered protein binding, or renal or hepatic impairment) were outside the scope of this first comparative PK evaluation and will need to be addressed before feralconazole's IV-to-oral switch strategy can be considered clinically validated.

Conclusion

Feralconazole's amorphous solid dispersion oral capsule achieves an absolute bioavailability of roughly 65% relative to the cyclodextrin-solubilized intravenous solution, with a terminal half-life essentially unchanged between routes and only a modest, non-restrictive food effect. That combination — incomplete but consistent absorption, route-independent disposition, and food tolerance — is close to what a clinically usable IV-to-oral switch formulation needs, even though it falls short of the near-complete bioavailability that isavuconazole's prodrug strategy achieves. High and concentration-independent plasma protein binding (98.6%) places feralconazole squarely within the range expected for this drug class and flags hypoalbuminemia correction as a priority for the pharmacokinetic studies that should follow in critically ill and immunocompromised patients, the populations in whom this drug is ultimately intended to be used.

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