Optimizing antifungal treatment through pharmacometrics: dosing considerations to enhance outcome

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Optimizing antifungal treatment through pharmacometrics: dosing considerations to enhance outcome

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Contents

Chapter 1

General introduction and scope

1.1 Invasive fungal diseases

Fungi, a distinct large group of micro-organisms, are ubiquitous in the environment. They are present in the air, soil, on plants and trees, indoor surfaces, and even on human skin, and mucosa [1]. Among approximately 6 million fungal species on Earth, about 0.01% are known to infect humans [2]. Fungi can easily spread to humans by direct or indirect contact, or simply by inhaling fungal conidia from the air. Invasive fungal diseases are diseases caused by fungal infections where fungi invade human tissue, germinate, and establish themselves, resulting in a prolonged illness. Invasive fungal diseases are commonly considered to be a higher severity of systemic and deep-seated fungal infection, even though from a microbiological perspective, a common, local, mild, self-limiting superficial fungal disease can also be invasive [3]. Over 150 million annual cases of severe fungal infections occur worldwide, resulting in 1.7 million deaths every year [4]. The number of people who die from the top 10 invasive fungal diseases is even higher than those dying from tuberculosis [5] or malaria [6]. Despite recent progress in the diagnosis and management of invasive fungal diseases, the mortality rate is still unacceptably high, varying between 20% and 95%, depending on the infection type and the patient population. The most common fungal pathogens are yeasts, such as *Candida spp.* and *Cryptococcus spp.*, and molds, such as *Aspergillus spp.* and *Mucorales spp.*, together accounting for more than 90% of reported fungal-related deaths [7].

As first-line defense humans have skin and mucosal membranes to prevent fungi from invading, as well as immune responses to restrict the spread of the invaded fungi and clear them before they can cause serious illness [8]. Such a defense system can be broken if any of these functions are disturbed. The invasive fungal disease mostly impacts individuals with profound immunodeficiencies, such as hematology patients receiving chemotherapy, intensive care unit patients with viral infection (e.g. influenza or COVID-19) [9, 10], HIV/AIDS patients, patients on immunosuppression, for instance, hematopoietic stem cell or solid organ transplants, patients on long-term glucocorticosteroid therapy, or patients with primary immunodeficiencies such as chronic granulomatous diseases. Among these patients, patients with hematological malignancies such as leukemia and lymphoma are particularly vulnerable to invasive fungal diseases and therefore have been considered the targeted population of the novel antifungal drug development for treating invasive fungal disease (IFD) [11]. Common treatment strategies for hematological malignancies involving antineoplastic chemotherapy, stem cell transplantation, as well as the new targeted and immunotherapeutic therapy [12], often induce neutropenia, which weakens the immune response, thereby increasing the risk of invasive fungal diseases.

1.2 Current antifungal treatment options and challenges

The current antifungal treatments are categorized into four groups based on their mechanism of action: polyenes, flucytosine, azoles, and echinocandins. Among

these, azoles are by far the most widely used antifungal agents in preventing and treating fungal infections owing to their broad-spectrum activity. Azoles are fungistatic. They inhibit fungal growth by blocking the biosynthesis of ergosterol, an essential component of the fungal cell membrane, by inhibiting the fungal cytochrome P450 enzyme lanosterol 14α-demethylase. Fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole are frequently used triazole antifungals. Even though they are recommended as the first-line prevention or treatment of invasive candidiasis or aspergillosis [13], treatments with triazole antifungals come with a few challenges, including numerous drug-drug interactions via inhibition or induction of human cytochrome P450 (CYP) enzymes (voriconazole and itraconazole), erratic absorption resulting in inadequate exposure (itraconazole tablets and posaconazole oral suspension), saturable metabolism (voriconazole) causing drug accumulation and toxicity, such as QT prolongation (all triazoles), hepatotoxicity (itraconazole and voriconazole and posaconazole), and neurotoxicity (voriconazole). As for all triazoles, exposure-response relationships are established, these factors may impact drug efficacy or toxicity. To address this, it is crucial to understand the pharmacokinetics of triazole agents.

1.3 Population pharmacokinetic modeling and simulation

Population pharmacokinetic modeling is a well-established method to describe the concentration-time profile of a drug in the body, in which data from all individuals in a population are analyzed simultaneously using a nonlinear mixed-effects model. “Nonlinear” refers to the nonlinearity of the concentration related to time and model parameters. “Mixed-effects” refers to the combination of two types of parameterization, i.e., “fixed effects” and “random effects”. “Fixed effects” applies to parameters that do not vary across individuals. “Random effects” applies to parameters that vary across or within individuals, which is often referred to as variability [14]. The fixed effects determine the pharmacokinetic profile of the typical individual from the population. The random effect determines how each individual’s pharmacokinetic profile deviates from the typical individual. Covariates in the population pharmacokinetic analysis are variables that are measurable and considered to have a potential relationship with the pharmacokinetic parameters in the model, such as weight, age, sex, race, renal/hepatic function, and concomitant medications. A primary goal of population pharmacokinetic modeling is to screen and quantify the impact of covariates that explain (part of) the inter-individual variability. Once the population pharmacokinetic model is developed, we can use model-based simulations to evaluate and optimize drug dosing. During this process, scenarios with various combinations of relevant covariates can be simulated under the standard dose to identify scenarios that can put patients at risk for overdosing, leading to toxicity, or underdosing, leading to therapeutic failure. Once hazardous scenarios are identified, alternative dosing schemes can be simulated to select and propose an optimal regimen.

In contrast to the non-compartmental pharmacokinetic analysis, population

pharmacokinetic modeling uses more complex mathematical and compartmental methods during model development and optimization, therefore often requires more time and effort. Yet the effort often pays off. Unlike the non-compartmental pharmacokinetic analysis, population pharmacokinetic modeling requires neither a stringent study design nor rich concentration-time data, which enables analyzing clinical data collected in a setting where rich data are not available, such as the concentration data from phase 2 and 3 trials, therapeutic drug monitoring, or opportunistic sampling. In fact, it may even be beneficial for the population pharmacokinetic modeling to have variability in sampling times. As population pharmacokinetic modeling can accommodate flexible study designs, it enables integrating concentration-time data across studies of various sampling schedules, formulations, and populations, to explore new research questions and derive more convincing conclusions by making the maximum use of the available information. For example, many marketed drugs are supplied with multiple formulations while most pharmacokinetic studies only analyze one formulation. With population pharmacokinetic modeling, pharmacokinetic data, regardless of whether rich or sparse, from patients receiving various formulations can be analyzed simultaneously and provide a comprehensive overview of the differences in the pharmacokinetic feature among various formulations. Such a quantified pharmacokinetic overview can provide insight into the pros and cons of each formulation, which serves as a reference for clinicians when prescribing a drug with multiple formulations. In addition, population pharmacokinetic modeling allows the exploration of extrapolation potential from one population to another. In case the extrapolation fails, an integrated analysis combining both populations can provide insights into which pharmacokinetic parameter(s) caused the difference and to what extent they are different from each other.

1.4 Oral absorption

Ninety percent of the global market share of drugs intended for humans comes as an oral formulation [15]. It is the most preferred administration route, because of the convenience which yields high patient compliance. Bioavailability is the most important pharmacokinetic parameter for oral absorption, as, together with clearance, it is the main driver of drug exposure. Bioavailability is impacted by many factors, including physicochemical properties of the drug (e.g., particle size, solubility, charge state, and permeability), drug formulation, and (patho)physiological characteristics (e.g., gastrointestinal pH, intestinal motility, and luminal water volumes) which may be impacted by concomitant food intake and biorhythm. As a result, high intra- and interindividual variability are not uncommon for bioavailability. Given that the oral route is the preferred administration route for long-term prophylaxis of invasive fungal diseases and considering the high mortality of breakthrough invasive fungal diseases that may result from under-exposure, bioavailability is of particular importance for these drugs. Therefore, identifying and quantifying factors that explain the variability of bioavailability for the antifungal drugs, is vital to guide adequate and safe dosing,

especially for those oral formulations with erratic absorption.

In theory, nonlinear pharmacokinetics can occur in all processes of absorption, distribution, metabolism, and excretion which involve enzymes or carrier-mediated transport. Intestinal metabolism and interaction with the intestinal transporters are common perpetrators causing saturated absorption. In addition to these, the exposure of poorly soluble weakly basic compounds can also exhibit a less-than-proportional increase with the increasing dose. This is because such compounds often dissolve incompletely in the stomach and the undissolved part subsequently transfers to the small intestine and acts as nuclei/seeds resulting in rapid precipitation under the increased pH, further resulting in unabsorbed drug excretion. In this case, when such compounds are given an increased dose, a higher fraction of precipitation and unabsorbed drug excretion would occur, manifesting a negative dose-dependent bioavailability [16]. If such dose-dependent nonlinear bioavailability is properly captured, dividing the same daily dose into a higher frequency can be a new strategy to ensure effective exposure. However, possibly limited by the narrow range of available dosages, such nonlinearity is rarely characterized in the published pharmacokinetic models. One prime example is posaconazole oral suspension.

Although drug absorption is a very complex process through numerous potential interactions, many published population pharmacokinetic studies adopted simple empirical absorption models with the assumptions of zero or first-order absorption rate with or without lag time. This is partly because for many marked oral drugs, the absorption is rather fast and the samples collected during the absorption phase are often relatively limited to inform a more complex profile. To determine the absorption kinetics, one may examine the plot of logarithmic concentration *versus* time for the population and make a decision from there, e.g., a first-order absorption model. This approach, however, may mask some misspecifications, and with the increased sampling frequency during absorption, the complexity of drug absorption becomes obvious and the misspecification could be seen from the diagnostic plots. Sometimes it might initially seem that a simple first-order absorption model is sufficient by inspecting the data, but, upon closer examination of the diagnostic plots, a more complicated absorption profile may be hidden. An inappropriate absorption model can result in the misspecification of the disposition model, as well as inflating the inter-individual variability and residual unexplained variability, risking an erroneous prediction of the dosage regimen. Therefore, it is essential to pay close attention to the absorption phase of the diagnostic plots and optimize the absorption model when characterizing the pharmacokinetics of oral drugs, particularly those with erratic absorption profiles. In practice, we commonly encounter perplexing absorption features in drugs with progressive dissolution along the gastrointestinal tract followed by subsequent intestinal absorption, gradual absorption delay, saturable absorption, enterohepatic recirculation, etc. More flexible empirical modeling strategies have been established to describe various atypical absorption profiles. This includes a simultaneous or a sequential combination of zero-order and first-order absorption,

transit compartment absorption as an alternative to the lag time model in describing absorption delay (Erlang distribution function [17] or estimation of an optimal number of transit compartments [18]), Weibull-type absorption, absorption window-type with or without Michaelis-Menton absorption, time-dependent absorption rate, and inverse Gaussian density input-function [18, 19].

1.5 Obesity

The prevalence of obesity (body mass index [BMI] ≥30 kg/m^2) nearly tripled over the past 50 years with 39% of the world's adult population classified as overweight (BMI ≥25 kg/m^2), and 13% classified as obese [20]. Obesity impacts not only patients' health, leading to a myriad of comorbidities, but also the management of these diseases [21]. Obese individuals were reported with an increased risk to develop infections, including fungal infections [22-24]. Worse clinical outcomes were observed in obese patients with candidemia compared with non-obese patients [25]. Altered gut permeability, gastric emptying, cardiac output, liver- and renal capacity were demonstrated in obese and particularly morbidly obese individuals, which may impact drug absorption, distribution, metabolism, and excretion, thereby altering the pharmacokinetic profiles for drugs in this population [26]. In practice, unlike other special populations including children (pediatrics), the elderly (geriatrics), and pregnancy (obstetrics), the obese are often left out of pre-marketing clinical trials by the regulations. As a result, therapeutic protocols for obese patients are often lacking.

Obesity is associated with underdosing in the majority of antimicrobials, which can potentially lead to prophylactic or treatment failure [24, 25, 27]. There are a few commonly accepted assumptions to *a priori* predict the impact of obesity on drug pharmacokinetics. Lean body weight has been considered the preferred descriptor of clearance for obese individuals, but it was demonstrated to not be justified because there is unfortunately no size descriptor that can predict clearance for all drugs, even though total body weight appears to be the primarily selected descriptor for clearance based on the hitherto published studies [28]. The volume of distribution is often assumed to be larger in the obese population for lipophilic drugs, but not for hydrophilic drugs. This assumption does not stand for all circumstances as the volume of distribution is often (slightly) larger for hydrophilic drugs, while a high inter-drug variability was reported for lipophilic drugs [28]. CYP3A4 activity is usually presumed to be suppressed, while UDP-glucuronosyltransferase (UGT) activity is presumed to be increased in obese individuals [28]. These two assumptions only consider changes in the activity or abundance of hepatic enzymes resulting from obesity-related changes, but ignore the change in plasma protein binding, hepatic blood flow, and drug extraction ratios and thus fail to be generalizable to all drugs. It is also believed that the glomerular filtration rate is higher in obese *versus* non-obese populations, due to an increased renal blood flow and increased number and/or efficiency of functional nephrons. However, this assumption does not take renal diseases, altered transporter-mediated secretion, or reabsorption into consideration,

therefore also failed to be generalized to all scenarios [28]. As listed above, quite some commonly accepted assumptions to a *priori* predict the impact of obesity on drug pharmacokinetics are not generally valid. Considering the high mortality of invasive fungal diseases, it is necessary to investigate the pharmacokinetic changes of the commonly used antifungal drugs in obese *versus* non-obese populations and to identify predictive covariates to guide dosing.

1.6 Aims and scope of this thesis

The principal aim of this thesis is to better understand the pharmacokinetics of two triazole antifungals, i.e., posaconazole (**Chapters 2-4**) and fluconazole (**Chapter 5**), with a special focus on oral absorption and bioavailability, and therefore to guide dosing that maximizes the antifungal efficacy. For the pharmacokinetic study of posaconazole, we first had a comprehensive overview of what is currently known regarding the pharmacokinetics and pharmacodynamics of posaconazole (**Chapter 2**). Second, we integrate hitherto the most massive data from posaconazole oral suspension, delayed-release tablet, and intravenous infusion, in healthy volunteers, to simultaneously quantify the pharmacokinetics and clarify the pharmacokinetic differences among all these currently available formulations (**Chapter 3**). Third, we extended this integrated pharmacokinetic analysis to (mainly) hematological patients with the purpose of quantifying the influence of clinical characteristics, including Chinese ethnicity, on the pharmacokinetics of posaconazole for three formulations (**Chapter 4**). Last, we aim to bridge the knowledge gap of the impact of obesity on the pharmacokinetics of fluconazole. Using this knowledge, we proposed guidance on optimized fluconazole dosing for this special population (**Chapter 5**).

The current section outlines the general knowledge of invasive fungal diseases and the populations vulnerable to these diseases, current antifungal treatment options and challenges, basic concepts in population pharmacokinetic modeling and simulation, the importance of oral drug absorption in pharmacokinetic analysis, and the prevalence of obesity along with the dosing challenges in this population. This section points out that population pharmacokinetics serves as a powerful tool that allows us to understand one drug's pharmacokinetics of various formulations and among various populations. It also emphasizes the importance of characterizing the absorption feature in investigating the pharmacokinetics of oral drugs, and the demand for attention in quantifying the pharmacokinetics in special populations, such as obese individuals.

Posaconazole, a second-generation triazole, is playing a major part in preventing or treating invasive aspergillosis and mucormycosis. In **Chapter 2,** we reviewed the currently available knowledge on posaconazole pharmacokinetics, pharmacodynamics, major toxicity, existing resistance, clinical experience in special populations, and new therapeutic strategies to get a clear understanding of the clinical use of this drug. Through the literature search, we found that there is a plethora of

pharmacokinetic information on posaconazole oral suspension, while new information on the pharmacokinetics of both the delayed-release tablet and the intravenous formulation is emerging rapidly. These studies are however predominantly performed in one, and at most two of the three marketed posaconazole formulations, which exposed a knowledge gap for an integrated analysis that quantifies and compares the pharmacokinetics of all three formulations in parallel.

To circumvent the potentially confounding influence of pathological and clinical factors, we conducted an integrated population pharmacokinetic analysis in **Chapter 3,** which pooled by far the largest data in only a healthy population from all three formulations of posaconazole. In this analysis, we explored various empirical absorption models to characterize the absorption profiles of oral suspension and delayed-release tablets. To better describe the nonlinear saturable bioavailability in the oral suspension based on prior knowledge, the data was enriched by the meta-data from the literature. With the quantified absolute bioavailability and absorption rate for both oral formulations, including food effects, this study provided a quantitative reference when facing the formulation trade-offs.

Yet, these findings cannot be directly extrapolated to patients as the physiological function in patients is often more variable compared with the healthy population. The concomitant medications and complications are expected to further perplex the pharmacokinetics in patients. Moreover, the Chinese population was reported with a 25% lower clearance compared to the other global population based on clinical trials, but this has not yet been evaluated in clinical practice. Therefore, in **Chapter 4**, we added pharmacokinetic data from patients covering posaconazole three formulations to the rich data from the healthy volunteers and conducted an integrated analysis to investigate the impact of clinical characteristics and Chinese ethnicity on the pharmacokinetics of posaconazole in patients. Using these analytical results, licensed posaconazole dosage regimens were evaluated in patients under various possible clinical scenarios to guide dosing.

In **Chapter** 5, we investigated the pharmacokinetics of another very frequently used antifungal agent within the triazole family, fluconazole, which is mainly used to prevent and treat Candida infections. Despite that fluconazole has been marketed for 35 years, a dedicated study on the exclusive impact of obesity on the pharmacokinetics of fluconazole is still lacking. It is crucial to bridge this knowledge gap, particularly considering the expanding worldwide obesity pandemic and the high mortality associated with treatment failure from invasive fungal diseases, as well as the fact that commonly accepted assumptions are not generally valid to predict the impact of obesity on drug pharmacokinetics. In this study, we performed a prospective study in morbidly obese adults in comparison to non-obese adults using a semi-simultaneous design of oral and iv administration, which allows for estimating an accurate bioavailability and identifying descriptors for the inter-individual variability in fluconazole pharmacokinetics. Based on these findings, a dosing table was proposed for clinicians to treat *Candida* infections in obese adults.

In **Chapter 6**, the main findings from the previous chapters are summarized and discussed. The clinical significance is addressed. Furthermore, this section also outlines promising future opportunities on how to further improve antifungal therapy.

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Chapter 2

Pharmacokinetics and pharmacodynamics of posaconazole

This chapter is based upon:

Chen L, Krekels EHJ, Verweij PE, Buil JB, Knibbe CAJ, Brüggemann RJM. Pharmacokinetics and Pharmacodynamics of Posaconazole. Drugs. 2020 May;80(7):671-95.

Abstract

Posaconazole is typically used for preventing invasive yeast and mold infections such as invasive aspergillosis in high risk immunocompromised patients. The oral suspension was the first released formulation and many pharmacokinetic and pharmacodynamic studies of this formulation have been published. Erratic absorption profiles associated with this formulation were widely reported. Posaconazole exposure was found to be significantly influenced by food and many gastrointestinal conditions, including pH and motility. As a result, low posaconazole plasma concentrations were obtained in large groups of patients. These issues of erratic absorption urged the development of the subsequently marketed delayed-release tablet, which proved to be associated with higher and more stable exposure profiles. Shortly thereafter, an intravenous formulation was released for patients who are not able to take oral formulations.

Both new formulations require a loading dose on day one, to achieve high posaconazole concentrations more quickly, which was not possible with the oral suspension. So far, there appears to be no evidence of increased toxicity correlated to the higher posaconazole exposure achieved with the regimen for these formulations. The higher systemic availability of posaconazole for the delayed-release tablet and intravenous formulation caused these two formulations to be preferable for both prophylaxis and treatment of invasive fungal disease.

This review aims to integrate the current knowledge on posaconazole pharmacokinetics, pharmacodynamics, major toxicity, existing resistance, clinical experience in special populations, and new therapeutic strategies in order to get a clear understanding of the clinical use of this drug.

Key words Posaconazole Pharmacokinetics Pharmacodynamics

2.1 Introduction

Posaconazole (Noxafil®) is a systemic triazole antifungal drug derived from itraconazole and exerts the same antifungal mechanism of action as other azole derivatives [1]. Three formulations are currently available, namely an oral suspension (40 mg/ml), a delayed-release tablet (100 mg) and an intravenous formulation (18 mg/ml). The posaconazole oral suspension and delayed-release tablet are approved for patients of 13 years and older (USA) or adults of 18 years and older (Europe), while the intravenous formulation is licensed only in patients of 18 years and older. Posaconazole is mainly licensed for prophylaxis of invasive fungal diseases (IFD) in: 1) patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) which are expected to result in prolonged neutropenia and who are at high risk of developing IFD; 2) hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing IFD [2]. Additionally, it is approved for treatment of oropharyngeal candidiasis, for the treatment of patients with IFD that are intolerant to first line therapy, and as salvage treatment of IFD caused by rare pathogens, such as fusariosis, chromoblastomycosis, mycetoma and coccidioidomycosis [3].

2.1.1 Dosing

The posaconazole suspension is indicated to be dosed as 200 mg TID for prophylaxis or as 400 mg BID or 200 mg QID for treatment of refractory IFDs or for treatment of patients with IFD who are intolerant to first line therapy. The delayed-release tablet and intravenous formulation are indicated to be given as a loading dose at 300 mg BID on the first day and a maintenance dose at 300 mg QD thereafter.

2.1.2 Mechanism of Action

Similar to other azole derivatives, posaconazole inhibits the enzyme lanosterol 14α-demethylase and consequently inhibits the biosynthesis of ergosterol which is an essential component of fungal cell membrane (see in Fig. 1). This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane, thereby weakening the structure and function of the fungal cell membrane, which is considered to be responsible for the antifungal activity of posaconazole [2].

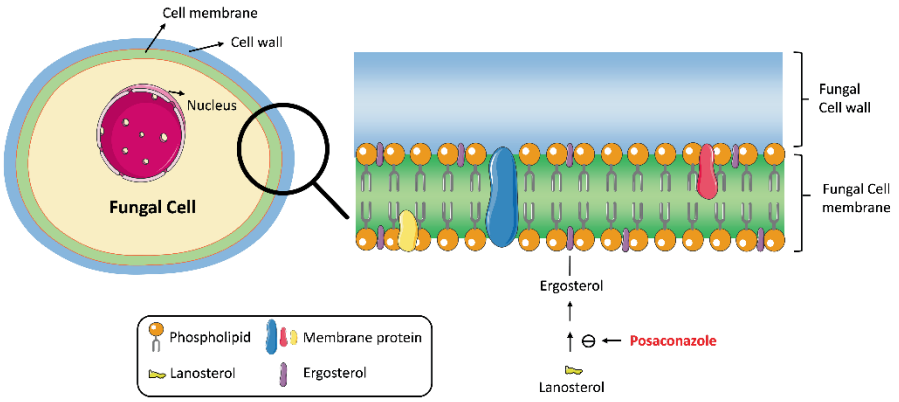

Fig. 1 Antifungal mechanism of action of posaconazole.

2.1.3 In Vitro Antifungal Activity

Posaconazole shows a wide spectrum activity against the majority of opportunistic pathogenic yeasts and molds in vitro, including the common pathogenic fungal species, such as *Candida* and *Aspergillus* species, but also against less common pathogens such as Mucorales and some Fusarium species [3]. According to European Committee on Antimicrobial Susceptibility Testing (EUCAST), the minimum inhibitory concentration (MIC) breakpoints for A. fumigatus are ≤0.12 mg/L for susceptible and >0.25 mg/L for resistant strains, 0.25 mg/L for A. terreus and 0.5 mg/L for *A. flavus, A. nidulans*, and *A. niger* [4]. The breakpoints of posaconazole against *C. albicans, C. dubliniensis, C. parapsilosis, C. tropicalis* are all defined as ≤0.06 mg/L for susceptible and >0.06 mg/L for resistant substrains. Higher resistant breakpoints of 0.25, 0.5 and 1.0 mg/L were demonstrated in *C. guilliermondii, C. krusei,* and *C. glabrata*, respectively [4].

2.1.4 *Aspergillus* resistance

Posaconazole showed potent dose-dependent in vivo antifungal activity in many animal studies on prophylaxis and treatment against *C. albicans*, *A. fumigatus,* and other uncommon fungal infections [5-13]. The area under the concentration-time curve (AUC) versus MIC, i.e. AUC/MIC, showed the strongest correlation with therapeutic success. Despite the dose-dependent killing, some strains of *A. fumigatus* have become fully resistant against azoles and this resistance has become of increasing clinical concern.

Acquired azole resistance in *A. fumigatus* is emerging globally and poses a therapeutic challenge [14, 15]. The majority of isolates with azole resistant phenotypes harbor mutations in the *cyp51A* gene, which codes for the enzyme lanosterol 14α-demethylase, or in the promotor region of this gene. Two routes of resistance

development have been proposed [16]. Azole resistance can develop in-host during treatment (patient route) or alternatively through exposure to azole fungicides in the environment (environmental route). Generally, the resistant mutations associated with these routes are different, as point mutations in locus G54, M220, G448, P216 in the *cyp51A* gene and non-*cyp51A* mediated mechanisms are mostly associated with in-host resistance development, while the L98H mutations in combination with a 34 base pair tandem repeat in the promoter region (TR_{34}/L98H) or Y121F/T289A in combination with a TR46 (TR_{46}/Y121F/T289A) are associated with the environmental route. Importantly, resistant isolates with environmental mutations have been found in patients without prior antifungal exposure. Exceptions to the categorization in resistance development routes were recently described as isolates with *cyp51A* point mutations have been recovered from the environment and azole-naive patients [17]. In addition, an isolate harboring a tandem repeat in the promotor region (TR120) was shown to have developed in-host through azole therapy [17, 18].

Case series indicate that azole resistance in *A. fumigatus* is associated with increased mortality rates [19-21]. Most resistance mutations affect the azole susceptibility of all the triazoles. But, as the triazoles are structurally different (e.g. long tailed and short tailed triazoles), different mutations may have various effects on the target binding of triazoles and thus mutations may have distinct effects on MIC values [22]. For example, TR_{34}/L98H often results in high itraconazole resistance with voriconazole, isavuconazole and posaconazole MICs being variable, while isolates with TR_{46}/Y121F/T289A have high resistance to voriconazole and isavuconazole with itraconazole and posaconazole being less affected. In most azole-resistant isolates, posaconazole retains the greatest *in vitro* activity, with MICs that are close to the resistance breakpoint. *In vivo* studies indicate that isolates with increased posaconazole MICs may still be treated with increased posaconazole exposure [7, 9]. As the azoles are the only drug class with activity against *Aspergillus* that can be administered orally, strategies are explored using higher than standard dosing to overcome resistance in selected patients and in infections by azole low-resistant isolates [23]. An increasing number of studies on different formulations, together with an extended clinical use of posaconazole, enriched our understanding regarding the pharmacology of this drug, but some discrepancies and controversial issues have also arisen. This review aims to integrate the current knowledge on posaconazole pharmacokinetics, pharmacodynamics, major toxicity, existing resistance, new therapeutic strategies, and clinical experience in special populations, in order to get a clear understanding of the clinical use of this drug.

2.2 Clinical Pharmacokinetics

The posaconazole oral tablet - not the marketed delayed-release tablet, but a premarketing formulation used before the oral suspension - showed dose-linearity in exposure up to a single dose of 800 mg, with saturation of absorption occurring above 800 mg in healthy volunteers [24]. Using simulation-based approaches it has

been proposed that the non-linear absorption might be attributable to the extensive precipitation of posaconazole in the small intestine due to the incomplete gastric dissolution in the pH shift from stomach to the intestine, caused by its high lipophilicity and weakly basic property [25, 26]. Hence, development of this oral tablet was not pursued and an oral suspension was brought to the market. Unfortunately, this suspension also demonstrated high inter-individual variability as typically patients that received the suspension did demonstrate dose-limited absorption above a daily dose of 800 mg with a highly variable and erratic absorption [27].

A gastric-resistant tablet formulation was subsequently designed for releasing posaconazole in the small intestine, in order to avoid the erratic absorption caused by the gastric conditions and to improve the systemic absorption. The systemic exposure after administration of this delayed-release tablet showed dose-linearity between 200 mg to 400 mg, while higher doses were not explored [28]. Finally, an intravenous formulation was designed for patients who do not tolerate oral medication. Dose-linearity was observed between doses of 200 mg and 300 mg whereas non-linearities were observed below 200 mg [29, 30]. Intravenous doses above 300 mg were not investigated. The exposure of these two new formulations still shows substantial interpatient variability [31-34].

The published population pharmacokinetic findings on posaconazole are discussed below and are summarized in Table 1. Model-independent findings on the clinical pharmacokinetics of posaconazole in healthy volunteers and patients are also discussed and are summarized in Table 2 and Table 3, respectively.

Table 1 Summary of population pharmacokinetic parameter values for posaconazole.

Authors	AbuTarif *et al* [38].	Kohl *et al.*[35]	Storzinger *et al.*[36]	Vehreschild *et al.*[37]	Dolton *et al.*[39]	Petitcollin *et al.*[40]	Iersel *et al.*[41]	Boonsathorn *et al.*[52]	Merk *et al.*[30]
Year	2010	2010	2012	2012	2014	2017	2018	2019	NA
Formulations	Sus	Sus	Sus	Sus	Sus	DR-tab[a]	DR-tab[b]	Sus and DR-tab[a]	Inj
Populations	AML/MDS	allogeneic HSCT	SICU	AML/MDS	HV, IMD (48%HSCT)	HM	HV, AML/MDS/ HSCT	IMD	HV, AML/MDS/ HSCT, clinical trials
Number of individuals	215	32	15	84	102 (20 HV and 82 patients	49	335(104 HV and 231 patients)	117 (children aged 5m-18y)	HV (67), AML/ MDS (166), HSCT (73)
Number of samples	702	149	270	643	905	205	5756	338 (96.4% Sus)	2322
Sample type	plasma	serum	serum	serum	plasma	NA	plasma	plasma	plasma
Absorption	NA	first-order	NA	first-order	first-order oral absorption with ALAG	first-order	sequential zero first-order	first-order	NA
k_a (h^{-1}) estimate (%RSE)	0.040	0.40 fixed	0.77 (35.6)	0.40 fixed	1.3	0.59 (15.0)	0.85 (7.8)	Sus, 0.20 (fixed); DR-tab, 0.59 (fixed)	—
Number of compartments	one	one	one	one	one	one	one	one	two
V/F (L) estimate (%RSE)	3290.0 (24.9)	2250 (6.9)	5280.0 (29.5)	2770.0 (6.6)	1100.0	420.0 (10.0)	393.0 (2.8), V only	201.7 (38.8)	V_c=61.6 (6.8), V_p=181.0 (4.5), absolute V
Elimination	NA	first-order	NA	first-order	first-order	first-order	first-order	NA	first-order
CL/F (L/h) estimate (%RSE)	65.1	67.0 (5.9)	195.0 (16.7)	42.5 (5.2)	30.2	7.3 (5.0)	9.7 (5.0)	15.0 (34.5)	7.8 (3.0), absolute CL
Others parameters	k_e (h^{-1})=0.020 fixed	—	—	—	ALAG (h)=1.8	—	D1 (h)=2.5 (3.5)	β_{dose}=99.0 (44.4)	Q=93.5 (9.3)

Authors	AbuTarif *et al* [38].	Kohl *et al.*[35]	Storzinger *et al.*[36]	Vehreschild *et al.*[37]	Dolton *et al.*[39]	Petitcollin *et al.*[40]	Iersel *et al.*[41]	Boonsathorn *et al.*[52]	Merk *et al.*[30]
IIV, %CV (%RSE)									
CL/F	—	26.9 (13.2)	51.8 (39.9)	25.3 (10.9)	46.4	24.2 (30.0)	37.9 (13.1), CL only	63.0 (23.9)	43.9 (11.2)
V/F	41.1 (9.01)	—	52.0 (53.3)	—	30.2	28.2 (32.0)	—	—	V_c=51.9 (72.5), V_p=22.0 (29.5),
k_a	—	—	—	—	53.4	—	57.5 (29.3)	—	—
Others	k_e=49.7 (10.8)	—	—	—	—	—	relative F=24.2 (26.7)	—	Q=35.2 (49.8)
IOV, %CV (%RSE)									
Relative F	—	—	—	—	23.6 (HV vs. patients)	—	21.4 (23.3)	—	—
Others	—	—	—	—	—	CL/F=31.9 (14.0)	k_a=71.1 (17.0); D1=48.6 (9.8)	—	V_c=47.2 (75.8)
Residual error, %CV (%RSE)									
Proportional	—	—	—	—	6.8 in HV, 53.8 in patients	14.8 (4.0)	—	47.3 (0.2)	—
Additive	—	—	—	—	—	—	0.42 (8.7) in phase 1 studies; 0.32 (10.3) in phase 3 study	0.02 mg/L (82.7)	—
Exponential	32.1 (8.74)	—	—	—	—	—	—	—	—
Unknown		42.0 (8.7)	11.6 (53.2), 2.8 (32.1)	23.2 (5.1)	—	—	—	—	0.39 (5.9) in HV, 0.47 (6.1) in patients

Authors	AbuTarif *et al* [38].	Kohl *et al.*[35]	Storzinger *et al.*[36]	Vehreschild *et al.*[37]	Dolton *et al.*[39]	Petitcollin *et al.*[40]	Iersel *et al.*[41]	Boonsathorn *et al.*[52]	Merk *et al.*[30]
Covariates (increase)	race (nonwhite vs. white), diarrhea, PPI use, GGT levels ≥2 × ULN, bilirubin levels ≥2 × ULN on V/F	diarrhea on V/F and CL/F	none	body weight on V/F, diarrhea and PPI use on CL/F	coadministration of phenytoin/ rifampin and fosamprenavir on CL/F, nutritional supplement on relative F (HV vs. patients)	none	dosing regimen (single dose vs. multiple dose) on CL/F, food intake on k_a, formulation (tablet A/B vs. tablet C/D) on relative F	none	body weight on V_p, disease status (patients vs. HV) on V_c and V_p
Covariates (decrease)	none	age on V/F	none	coadministration of chemotherapy on V/F	coadministration of metoclopramide, PPI, cocurrent mucositis and diarrhea on relative F (HV vs. patients)	none	concurrent of AML/MDS and body weight on relative F	cocurrent of diarrhea, coadministration of PPI on relative F (Sus vs. DR-tab)	none

[a]the marketed delayed-release tablet; [b]four trial delayed-release tablet formulations, including tablet A, tablet B, tablet C and tablet D (tablet D is the marked image);
ALAG, absorption lag time; AML, acute myelogenous leukemia; CL, clearance; CL/F, apparent clearance; CV, coefficient variability; D1, duration of zero-order absorption into the depot compartment; DR-tab, delayed-release tablet; F, bioavailability; GGT, gamma-glutamyl transpeptidase; HM, haematological malignancy; HSCT, hematopoietic stem cell transplant; HV, healthy volunteers; IIV, inter-individual variability; IMD, immunodeficiency; inj, injection; IOV, inter-occasion variability; k_a, absorption rate constant; k_e, elimination rate constant; MDS, myelodysplastic syndrome; NA, not available; PPI, proton-pump inhibitors; Q, intercompartment clearance; RSE, relative standard error; SICU, surgical intensive care unit; Sus, suspension; ULN, upper limit of normal; V, volume of distribution; V/F, apparent volume of distribution; V_c, central volume; V_p, peripheral volume; β_{dose}, estimated dose in mg/m^2 for suspension bioavailability to drop to half that of the delayed-release tablet;

Table 2 Summary of pharmacokinetic characteristics of posaconazole in healthy volunteers using model-independent methods.

Authors	Year	Posaconazole formulation	No. of subjects	Dosage (mg)	Single or multiple dose	Food status	AUC_{tf} (mg·h/L), mean (%CV)	T_{max} (h), median (%CV/range)	$t_{1/2}$ (h), mean (%CV)	C_{max} (mg/L), mean (%CV)	CL/F (L/h) for oral, CL for iv	V/F (L) for oral, V for iv	AR
Courtney et al.[24]	2003	Tab[a]	6	50	single	fed	2.3 (50.0)	6.3 (51.0), mean	15.9 (18.0)	0.11 (46.0)	23.3 (40.0)	511.0 (32.0)	—
			6	100	single	fed	6.1 (28.0)	7.3 (36.0), mean	18.3 (13.0)	0.24 (26.0)	16.5 (21.0)	431.0 (20.0)	—
			6	200	single	fed	10.4 (30.0)	5.8 (35.0), mean	24.5 (22.0)	0.33 (21.0)	20.5 (40.0)	674.0 (18.0)	—
			6	400	single	fed	19.4 (33.0)	6.3 (44.0), mean	24.1 (24.0)	0.61 (31.0)	21.8 (35.0)	781.0 (49.0)	—
			6	800	single	fed	47.0 (40.0)	6.2 (46.0), mean	24.4 (33.0)	1.3 (26.0)	19.2 (48.0)	594.0 (19.0)	—
			6	1200	single	fed	41.8 (42.0)	8.8 (85.0), mean	28.5 (26.0)	0.93 (28.0)	35.1 (73.0)	1341.0 (58.0)	—
			9	50 BID	multiple	fed	8.3 (36.0), AUC_{0-24}	$T_{max}1$=5.0 (12.0), $T_{max}2$=9.0 (34.0)	19.2 (16.0)	$C_{max}1$=0.46 (38.0), $C_{max}2$=0.37 (30.0)	13.5 (34.0)	365.0 (29.0)	6.6 (29.0)
			9	100 BID	multiple	fed	21.8 (40.0), AUC_{0-24}	$T_{max}1$=6.0 (40.0), $T_{max}2$=11.0 (16.0)	24.1 (20.0)	$C_{max}1$=1.1 (37.0), $C_{max}2$=1.0 (42.0)	10.3 (32.0)	343.0 (24.0)	6.9 (27.0)
			9	200 BID	multiple	fed	31.1 (26.0), AUC_{0-24}	$T_{max}1$=4.0 (12.0), $T_{max}2$=10.0 (19.0)	23.9 (26.0)	$C_{max}1$=1.8 (27.0), $C_{max}2$=1.4 (27.0)	13.9 (34.0)	467.0 (32.0)	7.6 (37.0)
			9	400 BID	multiple	fed	73.1 (20.0), AUC_{0-24}	$T_{max}1$=5.0 (12.0), $T_{max}2$=9.0 (32.0)	31.0 (46.0)	$C_{max}1$=4.2 (20.0), $C_{max}2$=3.2 (19.0)	11.5 (25.0)	486.0 (34.0)	8.3 (32.0)
Krishna et al.[50]	2012	Sus	15	100	single	fed	8.5 (25.0)	6.0 (5.0-12.0)	25.1 (35.0)	0.24 (18.0)	12.1 (26.0)	427.0 (39.0)	—
			15	100	single	fasted	3.0 (50.0)	4.0 (2.0-8.0)	29.2 (31.0)	0.084 (62.0)	34.0 (38.0)	1450.0 (54.0)	—
P07691_EMA [42]	NA	Sus	23	100	single	fed	8.0 (32.0)	5.0 (4.0-12.0)	26.2 (26.0)	0.25 (25.0)	12.9 (31.0)	468.0 (26.0)	—
P07691_EMA [42]	NA	DR-tab[b]	22	100	single	fasted	8.3 (33.0)	5.0 (3.0-12.0)	27.0 (27.0)	0.29 (40.0)	12.7 (37.0)	467.0 (25.0)	—
Krishna et al.[28]	2012	DR-tab[c]	10	200	single	fasted	23.0 (23.0)	4.0 (3.0-8.0)	25.1 (20.0)	0.78 (29.0)	8.8 (26.0)	NA	—
			9	400	single	fasted	42.8 (35.0)	5.0 (3.0-8.0)	26.1 (22.0)	1.3 (29.0)	9.6 (34.0)	NA	—

Authors	Year	Posaconazole formulation	No. of subjects	Dosage (mg)	Single or multiple dose	Food status	AUC_{tf} (mg·h/L), mean (%CV)	T_{max} (h), median (%CV/range)	$t_{1/2}$ (h), mean (%CV)	C_{max} (mg/L), mean (%CV)	CL/F (L/h) for oral, CL for iv	V/F (L) for oral, V for iv	AR
			8	200 QD	multiple	fasted	31.4 (32.0), $AUC_{0\text{-}tau}$	5.0 (2.0-8.0)	NA	1.8 (31.0)	NA	NA	3.14 (24.0)
			8	200 BID	multiple	fasted	30.6 (38.0), $AUC_{0\text{-}tau}$	4.0 (2.0-8.0)	NA	3.0 (38.0)	NA	NA	4.75 (28.0)
			8	400 QD	multiple	fasted	56.6 (54.0), $AUC_{0\text{-}tau}$	5.0 (0-12.0)	NA	2.9 (46.0)	NA	NA	3.16 (57.0)
Kraft et al.[48]	2014	DR-tab[b]	20	400	single	fasted	41.0 (47.0)	4.0 (2.0-8.0)	27.3 (37.0)	1.1 (43.0)	NA	NA	—
P07783_EMA [30]	NA	DR-tab[b]	13	300	single	NA	22.7 (46.0)	5.0 (3.0-6.0)	28.1 (25.6)	0.61 (37.9)	15.4 (45.8)	583.3 (36.0)	—
Kersemaekers et al.[29]	2015	Inj	9	50	single	NA	4.6 (31.0)	0.6 (0.5-0.7)	18.7 (34.0)	0.31 (30.0)	10.9 (25.0)	294.0 (39.0)	—
			9	100	single	NA	10.8 (27.0)	0.5 (0.5-0.5)	19.6 (16.0)	1.3 (27.0)	9.4 (23.0)	262.0 (22.0)	—
			9	200	single	NA	34.6 (52.0)	0.5 (0.5-24.0)	23.6 (23.0)	2.3 (29.0)	6.5 (32.0)	226.0 (38.0)	—
			9	250	single	NA	40.6 (39.0)	0.5 (0.5-0.5)	26.0 (23.0)	2.3 (26.0)	6.7 (29.0)	245.0 (33.0)	—
			9	300	single	NA	45.5 (26.0)	0.5 (0.5-1.0)	24.6 (20.0)	2.8 (30.0)	6.9 (27.0)	236.0 (17.0)	—
P07783_EMA [30]	NA	Inj	13	300	single	NA	42.9 (30.7)	0.5 (0.25-0.5)	28.8 (27.8)	4.3 (19.1)	7.6 (41.4)	294.6 (24.8)	—

[a]an unmarketed tablet formulation before releasing oral suspension, not a delayed-release formulation; [b]tablet D, the marketed delayed-release tablet; [c]tablet C, an unmarketed trial delayed-release tablet formulation; AR, accumulation ratio; AUC_{tf}, the area under the concentration-time curve from time zero (0 h) to the time of recovery of the final sample with a quantifiable concentration; $AUC_{0\text{-}tau}$, the area under the concentration-time curve during the dosing interval; BID, twice a day; CL, clearance; CL/F, apparent clearance; C_{max}, maximum concentration; CV, coefficient variability; DR-tab, delayed-release tablet; EMA, European Medicines Agency; F, oral bioavailability; Inj, injection; NA, not available; QD, once a day; Sus, suspension; $T_{1/2}$, terminal-phase half-life; Tab, tablet; T_{max}, the time to peak concentration; V, apparent volume of distribution; V/F, apparent volume of distribution;

Table 3 The summary of pharmacokinetic characteristics of posaconazole in patients using model-independent method.

Authors	Year	Posaconazole formulation	Diseases	No. of patients	Dosage (mg)	Sample day	AUC_{tau} (mg·h/L), mean (%CV)	T_{max} (h), median (%CV/ range)	$t_{1/2}$ (h), mean (%CV)	C_{min} (mg/L), mean (%CV)	C_{avg} (mg/L), mean (%CV)	C_{max} (mg/L), mean (%CV)	AR	CL/F (L/h) for oral, CL for iv	V/F (L) for oral, V for iv
Ullmann *et al.*[27]	2006	Sus	FN&IFD	24	400 BID	10	8.6 (86.0)	3.0 (0-12.5)	11.9 (3.0)	0.64 (98.0)	0.72 (86.0)	0.85 (82.0)	NA	283.0 (354.0)	2447.0 (421.0)
				19	600 BID	10	5.8 (71.0)	3.8 (0-10)	12.0 (3.0)	0.39 (64.0)	0.49 (71.0)	0.58 (71.0)	NA	179.0 (82.0)	4984.0 (919.0)
				18	800 QD	10	6.2 (71.0)	4.0 (2.4-12.5)	24.0 (2.0)	0.25 (100.0)	0.26 (72.0)	0.36 (74.0)	NA	215.0 (81.0)	5061.0 (903.0)
Gubbins *et al.*[53]	2006	Sus	autologous HSCT	7	200 QD	1	2.0 (56.1)	8.0 (4.0-12.5)	NA	NA	NA	0.12 (62.7)	—	NA	NA
				15	400 QD	1	3.0 (67.6)	8.0 (3.0-24.0)	NA	NA	NA	0.19 (68.1)	—	NA	NA
				7	200 QID	1	3.0 (37.3), AUC_{0-24}	4.5 (2.0-6.0)	NA	NA	NA	0.12 (50.3)	—	NA	NA
				7	200 QD	14.0 (42.9)	4.5 (64.4)	4.0 (1.0-6.0)	NA	NA	NA	0.26 (76.8)	2.7	59.4 (52.1)	NA
				14	400 QD	9.9 (23.2)	6.4 (50.0)	7.0 (3.0-12.0)	NA	NA	NA	0.35 (47.1)	2.4	90.4 (79.8)	NA
				7	200 QID	8.1 (13.6)	8.7 (37.9), AUC_{0-24}	10.3 (1.0-24.0)	NA	NA	NA	0.48 (40.6)	3.9	89.1 (58.8)	NA
Zhang *et al.*[54]	2016	Sus	LT-CF	7	829/day	≥5d	5.8 (0.25-15.8), AUC_{0-24}, median (range)	4.4 (0-7.8)	NA	0.19 (0-0.62), median (range)	0.23 (0.01-0.77), median (range)	0.31 (0.021-0.97)	NA	143.2 (32.3-3278.7)	NA
			LT-non-CF	12	862/day	≥5d	17.2 (4.3-63.8), AUC_{0-24}, median (range)	4.0 (0-11.8)	NA	0.47 (0.12-2.1), median (range)	0.59 (0.15-2.5), median (range)	0.70 (0.23-3.0)	NA	51.8 (13.6-216.3)	NA
Duarte *et al.*[31]	2014	DR-tab[a]	AML/MDS	20	200 BID	1	4.6 (34.0)	3.1 (1.9-4.1)	NA	0.16-0.88, range	NA	0.64 (33.0)	—	NA	NA
				33	300 BID	1	6.2 (28.0)	4.0 (1.8-8.1)	NA	0.44-1.6, range	NA	0.84 (28.0)	—	NA	NA

Authors	Year	Posaconazole formulation	Diseases	No. of patients	Dosage (mg)	Sample day	AUC_{tau} (mg·h/L), mean (%CV)	T_{max} (h), median (%CV/ range)	$t_{1/2}$ (h), mean (%CV)	C_{min} (mg/L), mean (%CV)	C_{avg} (mg/L), mean (%CV)	C_{max} (mg/L), mean (%CV)	AR	CL/F (L/h) for oral, CL for iv	V/F (L) for oral, V for iv
				19	200 QD	8	22.7 (51.0)	4.9 (2.0-9.2)	NA	0.19-1.7, range	0.95 (50.0)	1.3 (49.0)	2.2 (60.0)	NA	NA
				32	300 QD	8	35.0 (41.0)	2.2 (1.3-8.1)	NA	0.34-2.6, range	1.5 (38.0)	2.0 (33.0)	2.5 (37.0)	NA	NA
Cornely *et al*.[32]	2016	DR-tab[a]	AML/MDS/ HSCT	50	300 QD	8	37.9 (42.0), AUC_{tf}	4.0 (1.3-8.3)	NA	1.3 (50.0)	1.6 (42.0)	2.1 (38.0)	NA	9.4 (45.0)	NA
			HSCT	17	300 QD	8	44.8 (45.0), AUC_{tf}	4.1 (2.0-8.3)	NA	1.5 (49.0)	1.9 (45.0)	2.4 (43.0)	NA	8.1 (46.0)	NA
			AML/MDS	33	300 QD	8	34.3 (36.0), AUC_{tf}	2.2 (1.3-8.1)	NA	1.2 (47.0)	1.4 (36.0)	1.9 (32.0)	NA	10.1 (43.0)	NA
Maertens *et al*.[33]	2014	Inj	AML/MDS	20	200 BID	1	5.4 (29.0)	1.5 (1.0-4.0)	NA	—	—	0.99 (47.0)	—	NA	NA
				22	300 BID	1	8.2 (26.0)	1.5 (1.0-2.0)	NA	—	—	1.6 (61.0)	—	NA	NA
				15	200 QD	14	28.2 (51.0)	1.0 (1.0-4.0)	NA	0.96 (63.0)	1.2 (51.0)	2.0 (50.0)	3.6 (44.0)	NA	NA
				19	300 QD	14	34.3 (42.0)	1.5 (0.98-4.0)	NA	1.1 (50.0)	1.4 (42.0)	2.6 (39.0)	2.8 (31.0)	NA	NA
Cornely *et al*.[34]	2017	Inj	AML/MDS/ HSCT	49	300 QD	10	36.1 (35.0)	1.5 (0.98-4.0)	NA	1.1 (44.0)	1.5 (35.0)	3.3 (74.0)	NA	NA	NA
Sime *et al*.[55]	2018	Inj	ICU	8	300 QD	1	11.6, AUC_{0-24}	NA	23.0	0.22	—	1.7	—	16.8	529.1

[a]tablet D, the marked delayed-release tablet;

AR, accumulation ratio; AUC_{tau}, the area under the concentration-time curve during the dosing interval; AML, acute myelogenous leukemia;AUC_{0-12}, the area under the concentration-time curve from 0 to 12 h; AUC_{0-24}, the area under the concentration-time curve from 0 to 24 h; AUC_{tf}, the area under the concentration-time curve from time zero (0 h) to the time of recovery of the final sample with a quantifiable concentration; BID, twice a day; C_{avg}, average concentration; CF, cystic fibrosis; CL, clearance; CL/F, apparent clearance; C_{max}, maximum concentration; C_{min}, trough concentration; CV, coefficient variability; DR-tab, delayed-release tablet; FN/ IFD, persistent febrile neutropenia or craCtory invasive fungal infection; HSCT, hematopoietic stem cell transplantation; Inj, injection; LT, lung transplantation; MDS, myelodysplastic syndrome; NA, not available; QD, once a day; QID, four times a day; Sus, suspension; $T_{1/2}$, terminal-phase half-life; T_{max}, the time to peak concentration; V, apparent volume of distribution; V/F, apparent volume of distribution;

2.2.1 Absorption

The two relevant parameters for oral absorption are the absorption rate constant (k_a), describing the rate of absorption, and bioavailability (F), describing the extent of absorption. The k_a of the suspension was reported to be different in different patient groups and mostly ranged from 0.40 to 0.77 h^{-1}, which corresponds to an absorption half-life ($t_{1/2}$) between 0.90 and 1.7 h [35-37]. Both a slower absorption (absorption $t_{1/2}$ of 17.5 h) as well as a faster absorption (absorption $t_{1/2}$ of 0.55 h) with a delayed onset of absorption have been reported [38, 39]. High inter-individual variability (53.4%) was reported for the k_a upon administration of the posaconazole suspension [39]. For the delayed-release tablet, similar k_a values were reported (0.59 h^{-1} and 0.85 h^{-1}) [40, 41] with inter-individual variability in k_a (57.5%) being as high as for the oral suspension [41]. Food intake proved to be associated with an increase in k_a, but was not expected to have a clinically relevant influence, because it had no impact on bioavailability or steady-state exposure parameters [41].

The mean value for F for the posaconazole suspension and delayed-release tablet were reported to be around 50% in healthy volunteers [42, 43], but was found to be about 2.6 times lower in patients receiving the posaconazole suspension [39]. It has been shown that food intake and nutritional supplements increase the F by improving solubility and delaying gastric emptying, thereby enhancing posaconazole exposure. Higher gastric pH and gastrointestinal motility decrease F of the oral suspension by reducing the solubility and shortening gastric residence time [44-47]. Additionally, administering the posaconazole suspension via nasogastric tube showed approximately 20% decreases in exposure compared to oral administration in healthy volunteers [47]. In immunocompromised patients, coadministration of proton pump inhibitors (PPI) or metoclopramide, or the occurrence of mucositis or diarrhea were proven to reduce the F of posaconazole by 45%, 35%, 58%, and 45%, respectively, while administration with nutritional supplements could increase F by 129% [39].

The systemic exposure of posaconazole upon dosing of the delayed-release tablet formulation is less susceptible to the aforementioned gastric conditions than the suspension. Coadministration with antacids, PPIs, H2 receptor functional antagonists, or metoclopramide proved to have a non-clinically relevant impact on the F of posaconazole in a healthy population receiving the delayed-release tablet [48]. A high-fat meal could only modestly increase the posaconazole AUC by 50%, in contrast to a 400% increase in similar conditions for the suspension, even though the high-fat meal postpones the median time to peak concentration (t_{max}) with one hour [49, 50].

The posaconazole suspension exhibits a dose-dependent and saturable absorption profile, with more frequent dosing leading to higher exposure when the total daily dose is lower than 800 mg [46, 51]. This pattern was not observed in the delayed-

release tablet [28], due to the distinct differences in the gastrointestinal drug delivery features between these two oral formulations.

2.2.2 Distribution

Figure 2 shows posaconazole distribution in various human tissues and fluids after systemic administration [56-65]. This figure shows that posaconazole accumulates in peripheral tissues, especially in lungs, kidneys, liver, and heart [56, 66]. For instance, exposure in alveolar cells is about 32-fold higher than in plasma, although the exposure in the pulmonary epithelial lining fluid (ELF) is slightly lower than in plasma in health volunteers receiving the posaconazole suspension of 400 mg twice daily [58]. The concentrations in skin are similar to blood [59]. Posaconazole showed inconsistent distribution profiles in the cerebral spinal fluid (CSF) with CSF/serum levels ranging from 0.4% to 237% [62, 63]. It is unclear how cerebral inflammation impacts the permeability of the blood-brain barrier to further influence posaconazole exposure in CSF [62, 63]. Posaconazole concentrations in brain tissue have not been reported in humans, but in two murine models these concentrations were reported to be about half of serum concentrations [67, 68]. Based on the current evidence of posaconazole distribution in the central nervous system, there is no clear pharmacokinetic evidence to prioritize posaconazole in the treatment of cerebral infections.

Posaconazole is bound to the plasma proteins for more than 98%, predominantly to albumin [42], yet this does not limit extravascular distribution of posaconazole. With values of 61.6 L and 181 L for the central and peripheral volume of distribution (V_d) respectively, the V_d of posaconazole is relatively large [30]. When posaconazole is only administered orally, F cannot be estimated. In such studies apparent V_d (V_d/F) will be reported, which is inversely proportional to the value of F. Thus, the inter-individual variability in apparent V_d observed in patients receiving oral posaconazole is significantly affected by the F. In healthy volunteers, the V_d/F of the posaconazole suspension and the delayed-release tablet are about twice as high as the absolute V_d that was determined upon intravenous injection [29], which could be explained by the reported value of 50% for F. A compartmental pharmacokinetic model developed for patients with persistent febrile neutropenia or refractory IFD showed that the V_d/F of posaconazole suspension is 2447 L [27], which indicates a remarkably larger V_d/F than for the healthy population (427 L under fed and 1450 L under fasted conditions) [50]. Four population pharmacokinetic studies using non-linear mixed effect modeling confirmed this finding in other hematological patients receiving posaconazole suspension [35, 37-39]. The markedly larger V_d/F in the patient population might be in part due to the lower F caused by concomitant medication and multiple clinical factors. Patients from the surgical intensive care unit (SICU) exhibited the largest V_d/F (5280 L, compared to 1100 - 2770 L in hematological patients), which might be mainly caused by poor absorption resulting from the application of nasogastric tubes and/or by increased distribution to peripheral tissue due to capillary leakage

tissue due to capillary leakage and edema [36].

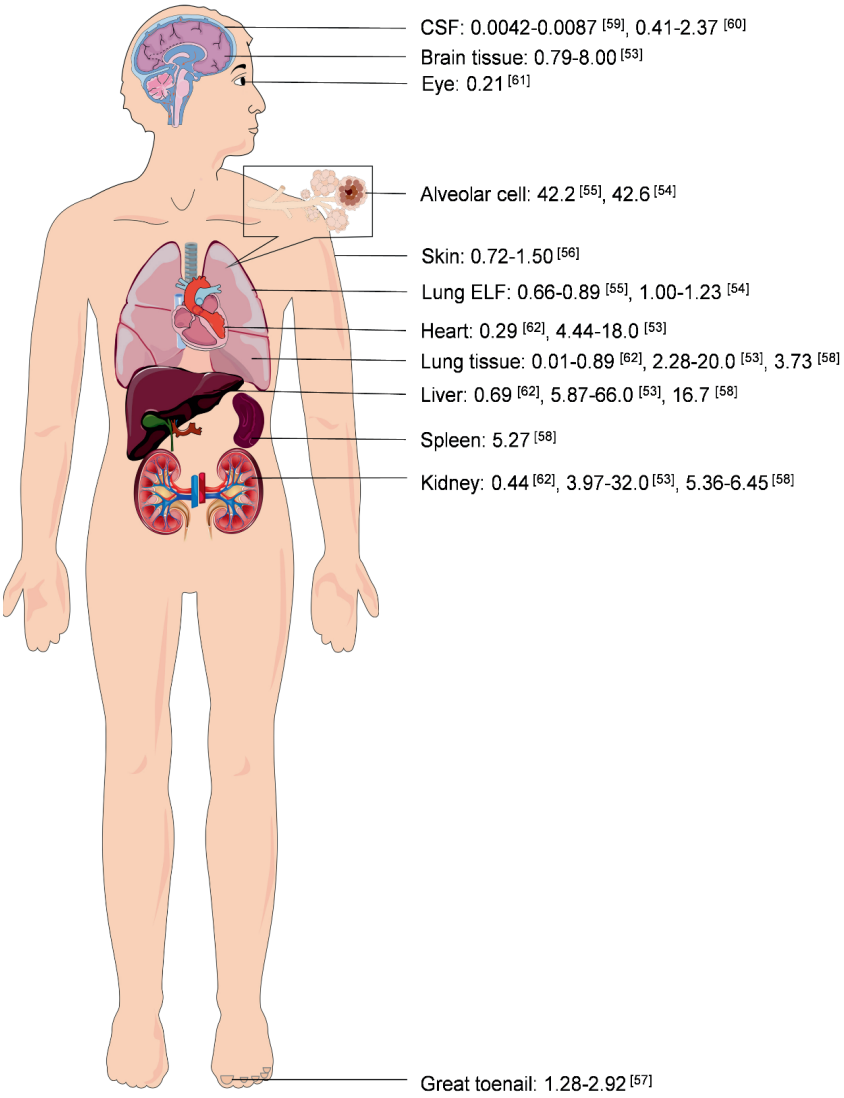

Fig. 2 Posaconazole distribution depicted as the ratios of tissue or fluid concentrations versus simultaneously measured plasma concentrations in different organs and tissues(tissue concentration unit: ng/g, fluid or plasma concentration unit: ng/mL). CSF = cerebrospinal fluid; ELF = pulmonary epithelial lining fluid

Inter-individual variability in posaconazole V_d was reported to be high among AML/MDS/HSCT patients [30]. Disease status (patients vs. healthy volunteers) proved to increase both central and peripheral V_d, moreover peripheral V_d was found to

increase with increasing body weight [30].

The delayed-release tablet formulation was found to exhibit a lower V_d/F than the suspension based on population pharmacokinetic analyses [35-41], but this is likely driven by the difference in F rather than by a true difference in V_d. In patients with AML/MDS receiving the oral suspension, ethnicity (non-white vs. white), higher weight, PPI use, occurrence of diarrhea, and high gamma-glutamyl transpeptidase or bilirubin levels (≥2 times the upper limit of normal) proved to significantly increase the V_d/F [37, 38], among which the impact of diarrhea and PPI use are likely driven by the decrease in F. In contrast, coadministration of chemotherapy has shown to decrease the V_d/F [37]. In patients receiving allogeneic HSCT, increasing age proved to be associated with decreases in V_d/F [35]. No variable was associated inter-individual variability in V_d/F for the delayed-release tablet [40, 41], which might be partly due to the weak influence from gastric condition on the extent of absorption.

2.2.3 Biotransformation and elimination

After administration of the posaconazole suspension, 77% of the dose is excreted by feces of which >66% is unchanged, while 13% of the doses is eliminated in urine of which <0.2% is unchanged [2]. Unlike other triazole antifungal agents, posaconazole is barely metabolized by cytochrome P450 (CYP). About 17% is glucuronidated by UGT1A4 and the remainder is eliminated unchanged [69, 70]. There are no major circulating metabolites. Nevertheless, posaconazole may still be impacted as victim drug by interactions with drugs that interact with UGT enzymes, like phenytoin, rifampin, and fosamprenavir [2]. Besides that, posaconazole is a potent inhibitor of CYP3A4 [2]. Clinicians and pharmacists should remember that the inhibitory potency of posaconazole is concentration, and thus formulation, dependent [71]. Several clinically relevant drug-drug interactions have been identified that require substantial empirical dose reductions of victim drugs (i.e. 30 - 50%), like cyclosporine A or tacrolimus. Adding to these examples are the interactions of posaconazole with new targeted therapies such as ibrutinib, venetoclax and ruxolitinib that make optimal management with these combinations challenging [72].

The posaconzole intravenous injection showed a decrease in clearance when increasing a single dose from 50 mg to 200 mg and this remained stable for doses of 200 mg and 300 mg [29]. which may be attributable to saturation of for instance enzyme or transporter involved in the elimination of posaconazole, which leads to the observed more-than-dose-proportional increase in exposure. Posaconazole clearance (CL) reported in a population pharmacokinetic analysis using combined data from both healthy volunteers and patients with AML/MDS/HSCT receiving an intravenous infusion appeared to be in line with these results reported from a clinical pharmacokinetic study in healthy volunteers (7.8 vs. 6.5 - 6.9 L/h) [29, 30]. The apparent clearance (CL/F) observed upon administration of the posaconazole suspension in patients is significantly higher than in healthy volunteers and differs among different

patient populations. Patients with persistent febrile neutropenia or refractory IFD, patients from SICU, and cystic fibrosis patients after lung transplantation appear to have high CL/F values (283.0, 195.0 and 143.2 L/h, respectively) [27, 36, 54], compared with those suffering from AML/MDS/HSCT (42.5 - 67.0 L/h) [35, 37, 38]. In general, the difference in F plays an important role in the substantial differences of posaconazole reported absolute clearance with intravenous formulation and apparent clearance with the oral suspension.

The posaconazole clearance upon administration of the delayed-release tablet showed a similar clearance profile in both healthy volunteers and patient populations [28, 40, 41]. The CL/F observed for the delayed-release tablet is twice as high as the CL of the intravenous formulation in healthy volunteers (15.4 vs. 7.6 L/h), which is also in line with F being estimated around 50% [30]. Two population pharmacokinetic models developed on data upon administration of the posaconazole delayed-release tablet demonstrated that CL/F is slightly lower, with values of 7.3 and 9.7 L/h in patients with hematological malignancies [40, 41]. Generally, the CL/F after administration of the oral suspension is higher than CL/F after administration of the delayed-release tablet, which could be explained by the lower F caused by the lower F of the suspension.

In patients receiving the posaconazole suspension, occurrence of diarrhea and coadministration of PPI or phenytoin/rifampin was associated with increases in posaconazole CL/F [35, 37, 39]. No clinically relevant covariate was identified with significant impact on CL/F or CL of posaconazole delayed-release tablet or iv formulation [30, 40, 41, 52].

Since posaconazole is metabolised by UGT and is a substrate for P-glycoprotein, inhibitors (e.g. verapamil, ciclosporin, quinidine, clarithromycin, erythromycin, etc.) or inducers (e.g. rifampicin, rifabutin, certain anticonvulsants, etc.) of these proteins may increase or decrease posaconazole plasma concentrations, respectively [3]. On the other hand, as a potent CYP3A4 inhibitor, posaconazole can induce large increases in exposure of CYP3A4 substrates as exemplified before. More details about drug-drug interactions for posaconazole can be found in previously published reviews [73-76].

2.2.4 Posaconazole descriptive pharmacokinetics

The AUC and peak concentration (C_{max}) after a single 100 mg dose of the posaconazole delayed-release tablet to healthy volunteers under fasting conditions were found to be similar compared to the oral suspension under fed conditions using the same dosage. This concentration is three times higher compared to the suspension under fasted conditions [42], which could be explained by the great impact of food and formulation on F for the oral suspension. The AUC and C_{max} of posaconazole upon intravenous administration are 2-fold and 7-fold higher, respectively compared to the delayed-release tablet after a single dose of 300 mg [30]. Posaconazole exposure

after administration of the oral suspension in healthy volunteers is about 2 - 3 times higher compared to hematological patients [42]. The steady-state exposures to posaconazole after administration of the delayed-release tablet or intravenous formulation are similar in patients with AML/MDS/HSCT, but are significantly higher than the suspension [32, 34, 77-79]. The variability in posaconazole average concentration (C_{avg}) upon administration of the oral suspension in patients with AML/MDS/HSCT is relatively high, ranging from 57 - 68% [77, 78]. As the variability in exposure (i.e. AUC or C_{avg}) upon dosing with the posaconazole delayed-release tablet and intravenous formulation in patients with AML/MDS/HSCT is smaller, i.e. 40% and 35% respectively [32, 34], it seems that absorption-related factors are attributable to the variation. A higher steady-state concentration was reported in HSCT patients compared to AML/MDS patients receiving posaconazole suspension and delayed-release tablet (1.47 vs. 0.58 mg/L for suspension, 1.87 vs. 1.44 mg/L for delayed-release tablet) [32, 77, 78], but not for the intravenous administration (1.56 vs. 1.47 mg/L) [34]. The accumulation ratio of upon dosing of the posaconazole suspension in patients is similar to the other two formulations (2.4 - 3.9 for suspension, 2.2 - 2.5 for delayed-release tablet, 2.8 - 3.6 for iv solution) based on the magnitude of AUC [31, 33, 53].

The mean tmax observed after administration of the posaconazole suspension ranged from 5.0 to 6.0 h in healthy subjects under fed conditions and 4.0 h under fasted conditions [50], which is similar to the value of delayed-release tablet (4.0 - 5.0 h) under fasted condition [24, 48]. The tmax of an intravenous dose is attained around the time of termination of infusion [28, 29, 32, 34]. The mean elimination t1/2 of the posaconazole suspension is (25.1 - 29.2 h), which is also comparable to the delayed-release tablet (27.0 - 28.1 h) in healthy volunteers [48, 50]. However, the mean t1/2 of the intravenous injection in healthy volunteers showed a dose-dependent prolongation from a single dose of 50 mg (18.7 h) to 200 mg (23.6 h), which can be explained by the aforementioned decreased clearance [29]. When giving a single dose from 250 - 300 mg, the elimination t1/2 of posaconazole intravenous formulation is similar to the other two oral formulations (24.6 - 28.8 h) [29].

2.3 Pharmacodynamics

Since neither one single dose nor one target concentration may be appropriate for all patients, researchers integrate the *in vivo* drug exposure and the *in vitro* susceptibility of pathogen against antimicrobial drugs, normally quantified as MIC, as a pharmacokinetic/pharmacodynamic (PK/PD) predictor for the *in vivo* antimicrobial efficacy. The relationship between the exposure to posaconazole and the corresponding antifungal response (PD) in relation to the pathogen susceptibility (MIC) has been verified in many preclinical studies.

2.3.1 Posaconazole PK/PD in preclinical studies

Prophylaxis

Posaconazole given as prophylactic therapy against pulmonary aspergillosis showed a dose-(and concentration)-dependent response in a neutropenic rabbit model and a neutropenic murine model [6, 11]. In the rabbit model, posaconazole was administered orally with 3 dosing levels of 2, 6, and 20 mg/kg/day 4 h before endotracheal inoculation with *A. fumigatus*. Rabbits receiving prophylactic posaconazole at all dosages showed a significant reduction in infarct scores, total lung weights, and organism clearance from lung tissue in comparison to those of untreated controls. A dose-dependent microbiological clearance of *A. fumigatus* from lung tissue in response to posaconazole was observed [6]. In the murine model, oral posaconazole was administered once daily with 5 dosing levels of 1, 4, 8, 16, and 32 mg/kg and mice were infected through instillation of the inoculum in the nares. A 24h-AUC/MIC ratio (AUC_{0-24}/MIC) of 37.4 (95% confidence interval, 7.1 - 196) was able to achieve half-maximal survival for preventing the pulmonary IFD caused by azole-resistant *A. fumigatus* for which the MIC against posaconazole was 0.5 mg/L [11]. Table 4 shows the posaconazole exposure-response relationships in various murine mode

Treatment

In addition to prophylaxis models, many preclinical PK/PD models have been established for the treatment of invasive candidiasis and aspergillosis [5-10]. The posaconazole exposure-response relationship was described using an inhibitory sigmoid E_{max} model based on an in vitro human alveolus model consisting of a bilayer of human alveolar epithelial and endothelial cells [8, 80]. EC_{50} with an AUC/MIC ratio of 2.2 and 11.6 was observed in endothelial and alveolar compartments of an in vitro model infected with *A. fumigatus*, respectively, and an AUC/MIC ratio of 100 was able to achieve near maximal decrease of galactomannan concentrations in both endothelial and alveolar compartments [8].

The relationship between AUC/MIC and the antifungal response to posaconazole were confirmed in three neutropenic murine models of invasive pulmonary aspergillosis and one non-neutropenic murine model of disseminated aspergillosis, all infected with *A. fumigatus* strains [7-10]. The AUC_{0-24}/MIC target associated with half-maximal antifungal response differs from model to model, with a ratio of the AUC/MIC of 321 when using mice mortality as endpoints [7] versus an AUC/MIC ratio of 167 when using the decline in serum galactomannan concentrations as end point [8], or an AUC/MIC of 179 and 53 when models using the fungal burden in the mouse lung are used as PD endpoint [9, 10]. The difference in pharmacodynamic endpoints, number and variety of fungal strains, inoculum size, and data analysis method, as well as drug source might contribute to the difference among these PK/PD targets. EUCAST accepted a PK/PD target of 167 - 178 AUC_{0-24}/MIC for infections

with *Aspergillus*. Using the licensed dose of 400 mg BID of the posaconazole oral suspension an AUC_{0-24} of 17.2 ± 14.8 mg·h/L (mean ± standard deviation [SD]) was achieved [27], suggesting 98% probability of target attainment for aspergillosis when MIC ≤ 0.015 mg/L [4]. If the delayed-release tablet or intravenous formulation is used in the licensed dose of 300 mg QD, an AUC_{0-24} of 34.3 ± 12.4 mg·h/L [31] and of 34.3 ± 14.4 mg·h/L (mean ± SD) [33] are achieved respectively, yielding 100% probability of target aggainment for a pathogen with a MIC ≤ 0.06 mg/L [4].

Table 4 Posaconazole AUC/MIC threshold corresponding to the EC_{50} for prophylaxis or treatment of IFD caused by different pathogenic fungi in murine models.

Model type	Year	Authors	Pathogens	Immune state	Infection type	No. of Strains	MIC (mg/L)	AUC_{0-24}/MIC	Pharmacodynamic endpoints	R^2
Prophylaxis	2015	Seyedmousavi *et al.*[11]	*A. fumigatus*	neutropenic	pulmonary	4	0.063 - >16	37	Survival rate	0.77
Treatment	2004	Andes *et al.*[5]	*C. albicans*	neutropenic	disseminated	12	0.015 - 0.12	169	Log_{10} CFU/ml of kidney homogenate	0.70
	2010	Mavridou *et al.*[7]	*A. fumigatus*	nonneutropenic	disseminated	4	0.031 - >16	321	Survival rate	0.89
	2011	Howard *et al.*[8]	*A. fumigatus*	neutropenic	pulmonary	4	0.12 - >8	167	Galactomannan index	NA
	2013	Lepak *et al.*[9]	*A. fumigatus*	neutropenic	pulmonary	10	0.25 - 8	179	Log_{10} CE/ml of lung homogenate	0.79
	2014	Lewis *et al.*[10]	*A. fumigatus*	neutropenic	pulmonary	1	0.5	53	Log_{10} CE/ml of lung homogenate	0.80
			[a]*R. oryzae*	neutropenic	pulmonary	1	2	63	Log_{10} CE/ml of lung homogenate	0.83

[a]now named *R. arrhizus*;
AUC_{0-24}, area under the 24h-concentration time curve; CFU, colony-forming unit; CE, conidial equivalents of fungal DNA; MIC, minimum inhibitory concentration; NA, not available; R^2, correlation coefficient

Posaconazole PK/PD in treating mucormycosis

Apart from the promising in vitro activity against Mucorales species, posaconazole also showed potential for preventing neutropenic mice from pulmonary mucormycosis by Rhizopus delemar [81], and disseminated mucormycosis by Absidia corymbifera (now Lichtheimia corymbifera) or R. oryzae (now R. arrhizus) [82]. When posaconazole is used for treatment of mucormycosis, an AUC0-24/MIC ratio of 63 proved to be the target that was associated with half-maximal effect of lung fungal burden based on a neutropenic murine model of pulmonary mucormycosis infected with R. oryzae [10]. Unfortunately, no controlled, adequately powered clinical efficacy trial is available to confirm this finding in humans. In clinical practice, the posaconazole suspension has been used as salvage therapy of mucormycosis and showed satisfactory efficacy in many cases [83, 84], which also indicates an encouraging prospect of the new formulation with higher drug exposure in this respect [85, 86]. Much like treatment of aspergillosis, for mucormycosis the delayed-release tablet or intravenous formulation are preferred due to the more favorable exposure attained with these formulations.

2.3.2 Posaconazole PK/PD in clinical studies

Although controversial, some studies suggest an exposure-response relationship for both prophylaxis and treatment of IFD in patients. As a certain amount of patients receiving the oral suspension showed low plasma concentrations [2, 79, 87-90], this indicates that therapeutic drug monitoring (TDM) may be needed to ensure adequate exposure [88, 89, 91-93].

Prophylaxis

In general it can be stated that target concentrations for posaconazole prophylaxis are still under debate [87, 94]. A lower boundary of steady-state C_{avg} of 0.7 mg/L for posaconazole is accepted as a target for prophylaxis by the FDA and in European guidelines [95, 96], which was supported by the analysis from two randomized, active-controlled clinical studies [87]. Posaconazole trough concentrations (C_{min}) proved to be well correlated with C_{avg} or AUC_{0-24} [32, 97]. Thus, C_{min} is also frequently used for TDM measures in practice and considered as a more conservative and practicable index [30, 98]. A recent meta-analysis indicated that a C_{min} of 0.5 mg/L could represent a clear margin separating successful from failed prophylaxis [99].

Treatment

For treatment purposes, posaconazole plasma C_{avg} ≥1.25 mg/L at steady-state proved to be associated with 75% successful response rates in patients with invasive aspergillosis and other mycoses, and therefore was considered as a cut-off value for IFD treatment [79]. The 2017 ESCMID-ECMM-ERS guidelines for management of *Aspergillus* disease recommends a slightly lower target trough concentration of 1.0 mg/L for treatment [100]. Both targets lack validation in a larger cohort.

2.3.3 Challenges of conventional PK/PD indices

Although PK/PD indices based on MIC are widely used for target exposures, there are some inherent drawbacks of these indices. Firstly, the PK/PD indices are mostly based on animal studies, but the species differences in pharmacokinetics are not taken into account. Secondly, the *in vitro* MIC is a static threshold value often established with poor precision, that is obtained in experiments with static antifungal concentrations, while it is not known how fungal susceptibility towards the antifungals is impacted by the dynamics in the exposure *in vivo*, nor how this impacts the development of resistance. By not considering the concentration-time course in a dosing interval, these indices are basically assumed to be independent of the drug pharmacokinetics. Finally, the indices do not take the hosts' immune response to the fungal infection into account, which may decrease the required *in vivo* drug exposure needed to obtain the same antifungal effect as in an *in vitro* setting.

Figure 3 illustrates how the currently applied PK/PD indices for antifungals relate to the pharmacological and physiological processes that occur *in vivo*. Upon antifungal administration a dynamic concentration-effect profile is obtained. Subsequently, it is the combination of the antifungal effect of the dynamic drug exposure as well as the immune system of the host that will determine the fungal burden. The fungal burden then drives the responses that are observed in preclinical or clinical studies. The PK/PD indices ignore most of this mechanistic information by summarizing the dynamic exposure into a single value and empirically establishing which of the available exposure metrics best correlates with the observed responses, using the MIC value obtained in *in vitro* experiments with static exposure and in the absence of host immune response. In the field of antibacterial drugs, more mechanism-based PK/PD models that do take this mechanistic information into account have been established to overcome the weaknesses associated with the use of the PK/PD indices [101-104]. Unfortunately, this approach has not yet been applied in the antifungal field. This should yield better target exposure values as well as improved between-species scaling of findings.

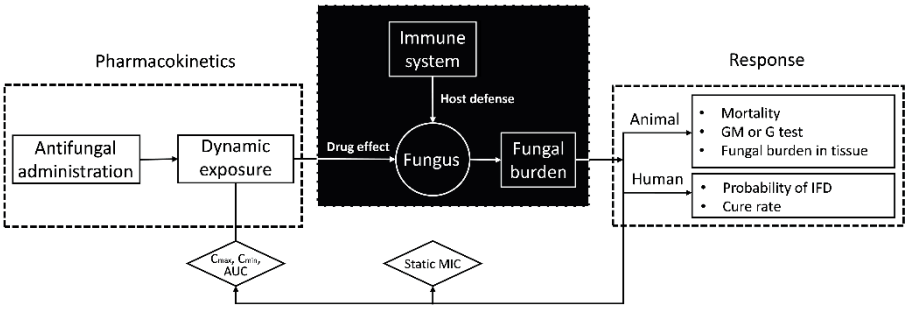

Fig. 3 Schematic illustration of the pharmacological and physiological processes driving antifungal drug response and how they link to the currently used PK/PD indices.

C_{max} = peak concentration; C_{min} = trough concentration; AUC = area under the concentration-time curve; MIC = minimum inhibitory concentration; GM test = detection of galactomannan; G test = detection of (1-3)-β-D-glucan; IFD = invasive fungal disease.

2.3.4 Toxicity

No clear relationship between posaconazole exposure and treatment-related toxicity has been identified to date [32, 87]. During the development process of the delayed-release tablet and the intravenous formulation, an upper toxicity limit of 3.75 mg/L was selected, which was derived from the 90th percentile of the exposure achieved from previous clinical studies that characterized safety for approval of the posaconazole oral suspension [32]. The most frequently reported adverse events during posaconazole treatment included gastrointestinal disorders, such as diarrhea, nausea, vomiting, and also hypokalemia, pyrexia, which are of little clinical concern and considered acceptable [2, 77, 78]. In the following sections we summarize the two posaconazole-related toxicities that are of most clinical concern, namely hepatotoxicity and cardiotoxicity.

Hepatotoxicity

Hepatotoxicity is usually considered a common adverse event (AE) of azole antifungal drugs. The occurrence of treatment-related increases in hepatic enzymes was 1 - 3% reported in 605 patients receiving the posaconazole suspension in two prophylaxis studies [77, 78]. Other treatment-related serious hepatotoxicities, such as hepatic failure and hepatocellular damage, appeared to be very rare (≤ 1%) among these hematological patients [77, 78]. The incidence of treatment-related abnormal liver function test (LFT) in 447 hematological patients receiving delayed-release tablets or intravenous injections was ≤ 2% which is similar to the suspension despite significant higher exposure [32, 34]. It was also reported that switching from suspension to delayed-release tablet can significantly increase posaconazole concentration more than 2-fold without worsening its hepatotoxicity [105]. Apart from hematological patients, posaconazole also showed a low occurrence of hepatotoxicity in patients with chronic pulmonary aspergillosis, refractory IFD and lung transplantation [106-108].

Some studies indicated that the incidences of LFT abnormalities are generally transient and reversible for long-term posaconazole use [2, 109, 110]. Most studies

found no correlation between posaconazole exposure and hepatotoxicity occurrence [108, 111-113]. Nevertheless, in 343 hematological patients receiving delayed-release tablets or intravenous injections, a posaconazole concentration of >1.83 mg/L was proven to be correlated with grade 3/4 hepatotoxicity using classification and regression tree analysis, although no association was found using logistic regression [114]. In general, even though the incidence is low, monitoring LFT is necessary and TDM together with dose adjustments or discontinuation and alternative medication should be considered when treatment-related liver toxicity is assessed.

Cardiotoxicity

QT interval prolongation is also a class effect of the azoles. Posaconazole was reported to be associated with a prolonged QT interval and other cardiac AEs, such as atrial fibrillation and torsades de pointes [77]. Treatment-related prolongation of the QT interval or corrected QT (QTc) interval occurred in 4% of 304 neutropenic patients receiving posaconazole suspension in one active-controlled prophylaxis study [77]. However, QT prolongation was not observed in healthy volunteers [2]. The incidences of the treatment-related atrial fibrillation and torsades de pointes are less than 1% [77]. There is no evidence of an increased risk of cardiotoxicity in hematological patients receiving posaconazole delayed-release tablets or intravenous injections. Surprisingly, the incidence rates of the treatment-related prolonged QT interval is slightly lower for these two new formulations (≤ 1%) [34].

Coadministration with CYP3A4 substrates, such as pimozide and quinidine, can increase the exposure of these drugs and result in a higher risk of cardiotoxicity, including QTc prolongation and torsades de pointes [114], therefore these drugs are contraindicated with posaconazole. Besides, posaconazole is also contraindicated to be used in patients receiving drugs that are known to prolong the QTc interval or those identified with potentially proarrhythmic conditions such as cardiomyopathy and QTc prolongation. Potassium, magnesium, and calcium should be corrected before posaconazole administration, in order to reduce the risk of posaconazole-related cardiotoxicity [2]. There are less safety concerns with respect to prolonged QT or QTc in patients with persistent febrile neutropenia or refractory IFD, patients with chronic pulmonary aspergillosis, and lung transplant patients [106-108]. No discernable correlation between posaconazole exposure and cardiotoxicity was found to date [30, 111].

2.3.5 Posaconazole resistance

Although the use of azole monotherapy is precluded in most patients with azole-resistant *Aspergillus* disease, a modest role of azole therapy may remain in infections caused by isolates with low-level azole resistance. If the azole MIC is close to the resistance breakpoint, dose escalation might be a feasible strategy provided that drug toxicity is avoided. The posaconazole MICs of azole-resistant *A. fumigatus* often remain close to the wild-type MIC distribution (i.e. MIC ≤0.5 to 1 mg/L) [115, 116]. Preclinical studies indicated that isolates with a posaconazole MIC of 0.5 mg/L can be treated successfully with increased exposure [7, 9]. The required AUC/MIC in patients to treat isolates with increased posaconazole MICs was calculated based on these experiments and bridged to human infections. Thus for each posaconazole MIC the required exposure was calculated. As the posaconazole AUC is linearly

correlated with C_{min}, target C_{min} values could be extracted from this correlation [97]. Thus, it is postulated that these isolates with relatively low MICs (but classified as resistant based on the EUCAST breakpoint) may be treated with augmented posaconazole dosing in order to achieve high drug concentrations [23]. One should bear in mind that clinical evidence on the efficacy of this strategy is absent. A major concern of a strategy using augmented dosing is the revelation of adverse events (AEs). One study evaluated the AE in patients with posaconazole high dosing regimen and incidental high posaconazole serum concentrations. This study concluded that the number of AEs in these groups were comparable to previous reports on standard dosing. A direct comparison between high dosing and standard dosing has not been reported [23].

2.3.6 New strategies for posaconazole targeted therapy

The finding that posaconazole accumulates in human peripheral blood mononuclear cells and polymorphonuclear leukocytes triggered an investigation on the impact of posaconazole-loaded leukocytes on the antifungal activity and functional capacity of different leukocytes [117-120]. High posaconazole intracellular concentrations did not show a significant impact on the functional capacities of human neutrophils and macrophages *in vitro* [118]. Natural killer cells also have proven to still be viable and they maintained their capacity under therapeutic concentration of posaconazole [120]. Similar results were also found in neutrophil-like leukocyte cells. Furthermore, an improved antifungal activity was observed both *in vitro* and in an *in vivo* mouse model with invasive pulmonary aspergillosis, which indicates the potential of posaconazole-loaded leukocytes as a novel antifungal strategy, in which leukocytes serve as a vehicle to target the infection site and further increase the antifungal effect [119]. Apart from this, these endogenous vehicles are supposed to be associated with less safety problems and are considered as a promising strategy for the prophylaxis and treatment of IFD.

2.4 Special populations

2.4.1 Patients with hepatic or renal impairment

Posaconazole showed slightly lower CL/F in patients with mild, moderate and severe hepatic impairment (corresponding to Child-Pugh class A, B and C, respectively) in comparison with healthy subjects after a single 400 mg dose of the oral suspension [121], which might be attributable to decreased metabolism by UGT1A4. The AUC was increased by 36% in patients with hepatic dysfunction compared to patients with normal hepatic function. Due to this minor change in the pharmacokinetics and the observed safety in patients with hepatic impairment, no dose adjustments are proposed for the posaconazole suspension in patients with hepatic impairment. This recommendation was directly applied to the later released formulations, without clear evidence on the influence of liver function on posaconazole pharmacokinetics nor the safety profile with these formulations in this population [2]. Future studies may still be needed to investigate the long-term pharmacokinetics and safety of all posaconazole formulations in patients with hepatic impairment.

No clinically significant difference in posaconazole CL/F or the exposure was

observed between patients with mild, moderate, and severe chronic renal disease (corresponding to creatinine clearance levels at 50-80, 20-49, <20 mL/min, respectively) and healthy subjects after a 400 mg single dose of oral suspension [122]. Posaconazole suspension also appears to be effective and well-tolerated in patients with refractory IFD and renal impairment (creatinine clearance <50 mL/min or serum creatinine level >2 mg/dL) [123]. Therefore, no dose adjustment was suggested in patients with mild and moderate renal impairment receiving the posaconazole suspension. There is still a necessity for monitoring of the symptoms of IFD just like other patients with IFD. This is due to the high variability in exposure of the oral suspension [3]. This recommendation was also directly applied to posaconazole delayed-release tablets without support by a clinical study [3]. The posaconazole intravenous formulation is not recommended for patients with moderate or severe renal impairment, because of the expected accumulation of the sulfobutylether-β-cyclodextrin excipient in the kidneys. However, from the experience with voriconazole, also containing sulfobutylether-β-cyclodextrin, we have learned that the benefits may outweigh the risk. In addition, the sulfobutylether-β-cyclodextrin appeared to accumulate by about six fold in kidney, but was not nephrotoxic itself [124-126]. Data on pharmacokinetics, efficacy and safety upon long-term posaconazole using are lacking in this special population, for which future studies are expected to fill the gap.

2.4.2 Obesity

For patients weighing ≥120 kg, the product label suggests to closely monitor for IFD due to the increased risk of lower posaconazole exposure [3]. Additionally, in patients with hematological malignancies, significantly lower trough concentrations were also observed between patients ≥90 kg compared to those <90 kg (0.65 vs. 1.31 mg/L), as well as between patients with body mass index ≥30 and those with a body mass index <30 (0.89 vs. 1.29 mg/L) receiving posaconazole delayed-release tablets [127]. The delayed-release tablet administration showed a significantly lower exposure and longer washout half-life in healthy obese subjects (weight of 116.8 ± 19.6 kg and 140.4 ± 32 kg, mean ± SD) compared to healthy normal-weight subjects (weight of 71.2 ± 8.2 kg and 67.9 ± 9.1 kg, mean ± SD) [128, 129]. The lower exposure can be attributed to an increased clearance and distribution volume [129]. In addition to this, the washout half-life is further prolonged by an increase in the already large distribution volume resulting from the extensive distribution of posaconazole into adipose tissue, which can also lead to a prolonged drug-drug interaction with of CYP3A4 substrates in obese patients [128, 129].

A recent population pharmacokinetic study in 16 obese patients receiving posaconazole by peripheral venous catheter, showed that a maintenance dose of 300 mg QD can only ensure target attainment in patients weighing less than 180 kg for prophylactic purpose (using C_{min} >0.7 mg/L as target). For patients with higher weights, 400 mg is required. For treatment purpose (using a C_{min} > 1.0 mg/L), the maintenance dose needs to be increased to 400 mg and 500 mg for patients weighing between 120 and 170 kg, and more than 170 kg, respectively [130].

2.4.3 ICU patients

Limited studies on the use of posaconazole were performed in patients admitted

to the intensive care unit (ICU). The posaconazole oral suspension given via nasogastric tube showed very low systemic exposure in 27 ICU patients with only 17% of the cohort achieving a steady-state C_{min} above 0.25 mg/L after a treatment of 400 mg BID or 200 mg QID, which indicates the posaconazole oral suspension to be unsuitable in this population and indicated the use of intravenous formulations [131].

A recent study reported the pharmacokinetic profiles of a single intravenous dose of posaconazole in 8 ICU patients [55]. Clearance and V_d were more than twice the value reported in healthy volunteers (16.8 L/h vs 6.9 L/h and 529 L vs 236 L, respectively) [29]. This could result from hypoalbuminemia increasing the unbound posaconazole, which can then distribute into the tissue and be eliminated by clearing organs, but unfortunately there are no studies available on the influence of hypoalbuminemia on the pharmacokinetics of posaconazole. The AUC and C_{max} in these patients are comparable to patients with AML/MDS, but lower than in healthy volunteers [29, 33, 55].

In brief, the posaconazole intravenous injection displays encouraging pharmacokinetic characteristics in ICU patients and further studies with larger cohorts are required to demonstrate the efficacy and safety of this formulation in this special population.

2.4.4 Pediatrics

While the posaconazole oral formulations are approved in patients older than 13 years (USA) or 18 years (Europe), the intravenous form is only labeled for patients older than 18 years, due to the potential toxicity to brain ventricle development observed in juvenile dogs [2, 30]. However, many studies have reported its off-label use in pediatric patients, which could be attributed to the promising efficacy and safety profile in adults [132-134]. A recent population pharmacokinetic model was developed for 171 pediatric immunocompromised patients aged between 5 month and 18 years receiving one of the oral formulations, with nearly 96% of the samples being obtained after administration of the suspension [52]. The estimated values of CL/F and V/F related to the delayed-release tablet formulation and standardized to a 70-kg individual are comparable to those reported in adults [40, 41]. These children showed a higher inter-individual variability on CL/F compared to that of adults (63.0% vs. 24.2% or 37.9%) [40, 41]. This might be partly attributable to the age-associated maturation of hepatic UGT1A4 [135].

A twice daily allometric dosing algorithm based on body-weight (index at 0.75) resulted in adequate posaconazole concentrations at day 10 in 12 children aged 3-16 years with chronic granulomatous disease [136]. In children aged ≤13 years, a bodyweight-based dosing regimen of the oral suspension of 4 mg/kg TID or body surface area-based regimen of 120 mg/m^2 TID, showed a considerable proportion of hematologic children to reach <0.7 mg/L steady-state plasma concentrations [137-140]. Therefore, higher initial dosing strategies of ≥20 mg/kg/day were recommended and expect to ensure adequate concentrations [141, 142]. Experience with the posaconazole delayed-release tablet in pediatric patients is limited. A model-derived dosing strategy was applied in 34 children and adolescents (range 5-17 years) receiving the posaconazole delayed-release tablet and more than 90% of the patients were reported to have steady-state trough concentrations above the target of 0.7 mg/L [134]. However, to implement such size-based dosing approaches in younger children, the delayed-release tablet displays an unattractive prospect as it

is indivisible and large in size. A new delayed-release tablet formulation of smaller dosage and size or a new oral suspension formulation with better bioavailability might benefit young children.

High variability in posaconazole concentrations was also reported in this population as a result of the erratic bioavailability for which TDM was recommended [138-141, 143]. Consistent with the previous findings in adult patients [37-39], diarrhea and concomitant PPI use also had a negative impact on the bioavailability of the suspension in children [52]. A population pharmacokinetic analysis in children illustrated the insufficient therapeutic target attainment even on the highest feasible dose of oral suspension in children with diarrhea and/or PPI administration [52]. Based on the model-based simulations, this study recommended different dosing regimens for different age groups for both prophylactic and treatment purpose in children patients aged <13 years. Due to the poor and saturable bioavailability of the suspension, the delayed-release tablet formulation is considered a superior choice compared to the oral suspension once the children are able to take it [52, 100, 134].

The establishment of pediatric target exposure is currently based on the concentration targets recommended in adults, which assumes that the same exposure will result in the same effect in adults and children. Although the susceptibility of fungi to antifungals can reasonably be expected to be the same in adult and pediatric patients, it still remains to be established whether differences in the developmental status of the immune system result in different required target concentrations *in vivo*. Differences in target concentrations could be likely, because despite the fact that the proportion of the target attainment was not high in children, the posaconazole oral suspension was demonstrated to be effective, safe and well-tolerated in preventing and treating IFD in immunocompromised children [137, 138, 140, 144-147].

2.4.5 Patients with cystic fibrosis

As the steady-state trough concentration for posaconazole delayed-release tablet is significantly higher than for the suspension both in cystic fibrosis (CF) (1.1 mg/L vs 0.19 mg/L) and in non-CF lung transplant patients (1.9 mg/L vs 0.47 mg/L) [54, 148], the delayed-release tablet form is considered a promising alternative for the suspension with satisfactory drug exposure and good tolerance. In lung transplant patients, patients with CF showed significant lower posaconazole concentrations compared to non-CF patients with both oral formulations [54, 148, 149], which can increase the risk of subtherapeutic concentration in this subgroup, especially for the suspension.

Higher posaconazole concentrations were found to be correlated with lower *Aspergillus* Immunoglobulin E levels [150]. Posaconazole oral formulations, especially the delayed-release tablet, exhibited satisfactory exposure in children (median age 13 years, range 3 - 17 years) with CF and was proven to be generally safe and well tolerated [151]. Overall, posaconazole delayed-release tablet appears to be a suitable antifungal agent in patients with CF due to the improved absorption and the wide intrinsic distribution into the lung tissue. Further studies are still needed to confirm the efficacy of posaconazole in CF patients.

2.5 Conclusions

Posaconazole is widely used for the prevention and treatment of IFD. As this drug is going off patent, new generic formulations are expected to enter the European market in the beginning of 2020, which will likely result in an increased clinical use due to anticipated price drops. The current review will help those that are less familiar with the use of posaconazole to better understand the behavior of this drug. We want to alert clinicians that especially the absorption profile and bioavailability of posaconazole appear to be highly dependent on the formulation, meaning that proposed dosages may not always be directly translatable to other formulations.

There is a plethora of pharmacokinetic information available for the oral suspension, while new information on the pharmacokinetics of both the intravenous formulation as well as the delayed-release tablet is emerging rapidly. These studies are predominantly performed in healthy volunteers and hematological patients. There is therefore an urgent remaining need for more (population) pharmacokinetic knowledge on both the critically ill patients as well as the pediatric population. For all populations three distinct pharmacological issues should be further explored:

1) differences in oral absorption profiles, bioavailability, and exposure of the three pharmaceutical formulations need to be clarified for each special patient population,

2) protein binding, the variability in protein binding, and its relation to PD must be investigated. This is typically relevant for populations with a high likelihood of altered protein binding such as critically ill patients, (pediatric) leukemic patients, and patients with renal failure,

3) more information on site specific penetration of posaconazole, specifically brain tissue, is needed. Now that higher and more predictable plasma concentrations are attained with the new formulations, it might be possible to achieve detectable brain concentrations thereby opening up treatment strategies, but also toxicological risks. Some neurological side effects have been described pointing towards an increased exposure in the brain [152], but this has yet to be confirmed.

There is a paucity of data related to the PD of posaconazole, especially on a mechanistic level. Past work on exposure response relationships needs to be revisited using unbound concentrations and taking into account dynamic exposure profiles. Simultaneously, the scientific community could invest in detecting new biomarkers that could provide useful information on the efficacy of treatment. Such markers should perform better than current measures of outcome that leave room for interpretation such as mycological response. These biomarkers should be subsequently linked to the dynamic pharmacokinetic profiles to define the PK-PD relations. Finally, knowledge should be gained on how to treat fungal disease with pathogens with attenuated MICs. Adaptive targets, i.e. targets based on the pathogens MIC, have been investigated in animal models, but its clinical utility needs to be validated. Ultimately, information on the hosts' immune response should also be utilized to complete the understanding on the interplay between pathogen, host, and drug to predict treatment outcome.

2.6 References

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Chapter 3

An integrated population pharmacokinetic analysis for posaconazole oral suspension, delayed-release tablet, and intravenous infusion in healthy volunteers

This chapter is based upon:

Chen L, Krekels EHJ, Heijnen AR, Knibbe CAJ, Bruggemann RJ. An Integrated Population Pharmacokinetic Analysis for Posaconazole Oral Suspension, Delayed-Release Tablet, and Intravenous Infusion in Healthy Volunteers. Drugs. 2023 Jan;83(1):75-86.

Abstract

Background Posaconazole is widely used for prophylaxis and treatment of invasive fungal diseases. Due to the limited and variable absorption of the initially available oral suspension, a delayed-released tablet (DR-tablet) and IV formulation were developed.

Objective This study characterizes the pharmacokinetics, including the absolute oral bioavailability (F), of all posaconazole formulations in healthy volunteers. Methods Data from 182 healthy volunteers with 3898 densely sampled posaconazole concentrations were pooled from 8 phase I clinical studies on the three formulations of various single and multiple dosage regimens between 50 and 400 mg. Analysis and simulations were performed using NONMEM 7.5.0. In the covariate analysis, the influence of food (fed *versus* fasted), nonlinearity, and for the DR-tablet, comedication (antacid, ranitidine, esomeprazole, and metoclopramide) were tested. Results A two-compartment model with respectively four and eight absorption transit compartments best described the profiles of the oral suspension and DR-tablet. For the suspension, both a food effect and a dose-dependent nonlinear F were quantified, resulting in lower F when fasted or at a higher dose. The typical F of the suspension at 100 mg and 400 mg was derived to be respectively 17.1% and 10.1% under fasted conditions and 59.1% and 49.2% under fed conditions. The absolute F of the DR-tablet was 58.8% (95% confidence interval [CI] 33.2-80.4%) under fasted conditions and approached complete absorption under fed conditions for dosages up to 300 mg. Food intake reduced the absorption rate constant of the suspension by 52.2% (CI 45.2-59.2%). The impact of comedication on the absorption of the DR-tablet was not statistically significant. Model-based simulations indicate that under fed conditions, the licensed dosages of the three formulations yield a steady-state trough concentration ≥0.7 mg/L in over 90% of healthy volunteers. About 35% of healthy volunteers who receive the licensed 300 mg DR-tablet under fasted conditions fail to achieve this target, while for the suspension this percentage varies between 55% and 85%, depending on the dose. Conclusion For both oral posaconazole formulations, we quantified F and absorption rate, including food effects, in healthy volunteers. The pharmacokinetic superiority of the DR-tablet was demonstrated under both fed and fasted conditions, compared with the oral suspension. The impact of food on the F of the DR-tablet was larger than anticipated, suggesting that administering the DR-tablet with food enhances absorption.

Keywords posaconazole, oral bioavailability, healthy volunteers

3.1 Introduction

Posaconazole is a triazole antifungal agent and is widely used for preventing and treating invasive fungal diseases (IFDs) [1-3]. Posaconazole is available in three formulations, namely oral suspension, delayed-release tablet (DR-tablet) and intravenous infusion (IV) [1, 3]. Erratic absorption, both in terms of rate of absorption and extent of absorption (i.e. bioavailability) was widely reported for the oral suspension [4, 5] with the exposure of this formulation also being sensitive to food intake and other gastrointestinal conditions, such as pH and motility [6, 7]. A DR-tablet was subsequently developed, which proved to be less sensitive to these factors and yielded a higher average exposure in patients compared with the oral suspension [4, 8-10]. Shortly after, an IV formulation was released for patients who are unable to take oral formulations.

Prophylactic failure against *Aspergillus* infections was reported to be associated with low exposure. A trough concentration (C_{trough}) ≥0.7 mg/L is included in the label as a target for preventing IFDs [11-13]. A treatment target of C_{trough} ≥1.0 mg/L or ≥1.25 mg/L was recommended in international guidelines [2, 14]. Both target concentrations for prophylaxis and therapy have, however, been subject to debate and it has been advocated to use pathogen susceptibility-dependent target concentrations [2].

In the clinical setting, switching from DR-tablet to oral suspension is sometimes needed in patients with dysphagia or in patients with a nasogastric tube when solid intake is not possible. Switching from the IV dosing to an oral formulation is usually necessary as step-down therapy for long-term therapy in an outpatient setting. To gain knowledge on the exposure being obtained with each formulation and to ensure equivalent exposure when switching formulations, it is important to understand and quantify the differences in the pharmacokinetics for all formulations.

Many studies have investigated the pharmacokinetics of one or two of the three marketed posaconazole formulations, but an integrated analysis comparing the pharmacokinetics of all three formulations simultaneously is still lacking. This study uses a population pharmacokinetic modeling approach to quantify the pharmacokinetics of all currently available posaconazole formulations, including the absolute oral bioavailability (F) of the oral suspension and DR-tablet, and the impact of food intake and comedication on absorption in healthy volunteers. Model-based simulations were used to illustrate our findings.

3.2 Methods

3.2.1 Data for analysis

In total, 3898 posaconazole concentrations (including 299 [7.7%] concentrations below the limit of quantification) densely sampled up to 168 h from 182 healthy volunteers pooled from 8 clinical studies, with different formulations, dosages

(ranging from 50 - 400 mg) and dosing schedules (i.e., single dose and multiple dose at different intervals), were included in the analysis. Six studies were performed by Merck & Co., Inc., i.e., P04975 [15], P07691 [16], P07764 [10], P07783 [16], P04985 [17], P06356 [18], and two studies in the Radboudumc, Nijmegen, the Netherlands [19, 20]. In a crossover study P04975, sixteen healthy volunteers received the oral suspension under both fasting and fed conditions with one subject dropping out and only being included under fasting conditions [15]. In this latter study, on the two occasions, subjects were considered as separate individuals, because individual identifying information was not available in the accessible data. Data characteristics per formulation and per study are summarized in Table 1 and Table S1, respectively.

Dosing scenarios for the oral suspension were limited to 100 mg under fed and fasted conditions and 400 mg only under fed conditions. To better describe the nonlinear saturable F based on the prior knowledge [5, 7, 21], the data were enriched with meta-data from literature. We searched PubMed for clinical trials which investigated the effect of high-fat food on the F or area under the concentration-time curve (AUC) under a single dose of 100 mg and 400 mg in healthy volunteers. In case that multiple studies met the criteria, studies with longer sampling duration and higher number of participants were selected. A value of 2.85 [15] and 4.91 [7] for the ratio of F between the fed and fasted condition at 100 mg and 400 mg, respectively, with the value at 100 mg being based on a previous non-compartmental analysis on one of the datasets (P04975 [15]) were included in our analysis. Moreover, given that not all combinations of dose and food status were available to assess the saturable F of the oral suspension, reported literature values on the AUC and food effect from other pharmacokinetic studies were used during model evaluation [6, 7, 15, 16, 19].

3.2.2 Population pharmacokinetic model

The population pharmacokinetic model was developed using the nonlinear mixed-effects modeling software NONMEM version 7.5.0 (ICON Development Solutions, Hanover, MD, USA) supported by Perl-speaks-NONMEM (version 5.2.6) with the Pirana interface (version 3.0.0, Certara USA, Inc, Princeton, USA) [22]. Data processing and visualization were performed with R 4.1.1 and RStudio 1.4.1717. Due to the long run times, the M1 method for which observations below the quantification limit (BQL) are discarded, was applied during model development after establishing that the estimation results were similar between the M1 and M3 methods for the base model. The M3 method, in which the likelihood is maximized for all the data and BQL concentrations are treated as censored, was used to fit the final model [23]. The first-order conditional estimation method with interaction and LAPLACIAN in combination with the stochastic approximation expectation maximization (SAEM) method were adopted for models using the M1 and M3 methods, respectively.

Table 1 Summary of the pharmacokinetic data included in this analysis

Characteristics		Suspension [15, 16, 19]	DR-tablet [10, 16]	IV [16-18, 20]
No. of studies		3	3	4
No. of subjects		75	67	74
Dosage (mg)	Single dose	100	100, 300, 400	50, 100, 200, 250, 300
	Multiple dose	400 bid[a]	300 qd[b]	NA
Duration of sampling after the last dose (h)	Single dose	168	168	48, 144, 168
	Multiple dose	12	48	NA
No. of concentrations		1028	1924	946
No. of BQL concentrations (%)		141 (13.7%)	110 (5.7%)	48 (5.1%)
No. of concentrations per subject, median (range)		13 (11-16)	13 (2-65)	12 (10-20)
Available covariates		food status	Food status, comedications (antacid, ranitidine, esomeprazole, metoclopramide)	NA

DR-tablet delayed-release tablet, *IV* intravenous infusion, *NA* not available, *BQL* below the quantification limit, *bid* twice daily, *qd* once daily
[a]Posaconazole oral suspension 200 mg once daily on day 1, 200 twice daily on day 2, 400 mg twice daily from day 3 to day 10
[b]300 mg bid on the first day followed by 300 mg qd

One-, two- and three-compartmental disposition models were evaluated. Various approaches were assessed to describe absorption for each oral formulation, including first-order absorption with and without absorption lag time, transit compartment models [24, 25], mixed zero-order and first-order absorption [26, 27], and a Weibull absorption function [27]. Separate values for F and absorption rate were estimated for the oral suspension and DR-tablet. Inter-individual variability (IIV) was assumed to be log-normally distributed, except for F for which a logit transformation was applied and a normal distribution for IIV was incorporated in the logit domain. Proportional, additive, and combined additive and proportional error models were assessed for residual unexplained variability. The structural and stochastic model selection was based on the difference in objective function value (OFV, i.e., -2 log-likelihood) with an OFV reduction of >3.84 (P <0.05) for nested models being considered statistically significant, on the physiological plausibility of the parameter estimates, on the relative standard error of parameter estimates being <50%, and on the goodness-of-fit (GOF) plots stratified by formulation and study.

Concentration nonlinearity on clearance (CL) was tested to investigate possible saturation of the elimination of posaconazole [18]. Dose nonlinearity on F was tested to investigate possible saturation of the absorption for the DR-tablet. Dose nonlinearity on F was included for the oral suspension with decreasing sigmoidal functions, with different values for the maximum F of the suspension ($F_{sus,max}$) and for

the oral suspension dose that could achieve half of the $F_{sus,max}$ ($D_{50,sus}$) under fed and fasted conditions (see Equation 1).

$$F_{sus,fed} = F_{sus,max,fed} \times \left(1 - \frac{Dose}{Dose + D_{50,sus,fed}}\right) \quad \text{(Equation 1)}$$

In which $F_{sus,fed}$ represents the population value of F for the suspension under fed condition, $F_{sus,max,fed}$ represents the maximum F of the suspension under fed condition, Dose represents the suspension dose that was given, $D_{50,sus,fed}$ represents oral suspension dose that could achieve half of the $F_{sus,max,fed}$ under fed condition. Assuming the literature value of 4.91 for the ratio of F between fed and fasted condition at 400 mg [7] and assuming that the reported ratio of 2.85 at 100 mg is the same at the maximum F (e.g., F at the lowest possible dose), a correlation was deducted between oral suspension dose that could achieve half of the maximum F under fasted condition ($D_{50,sus,fasted}$) and $D_{50,sus,fed}$ (see Equation 2).

$$D_{50,sus,fasted} = \frac{3249 \times D_{50,sus,fed}}{5597.4 + 5.871 \times D_{50,sus,fed}} \quad \text{(Equation 2)}$$

Among three studies administering the oral suspension under fed condition, two were confirmed to be administered with high-fat food [15, 19], while the third unpublished study was also deduced to be administered with high-fat food as the concentration profiles overlapped with the profiles of the other study with high-fat food at the same dosage [16]. In addition to the assessment of dose nonlinearity and the impact of food intake for the oral suspension described above, food intake was also tested as a covariate on the absorption rate. For the DR-tablet, food intake (fed or fasted) was also tested as a covariate on both the rate and extent (F) of absorption. In one study (P07764), the DR-tablet was administered alone or with antacid, ranitidine, esomeprazole, and metoclopramide according to a cross-over design [10], which was used for an assessment of the influence of these comedications on the rate and extent (F) of absorption. Additionally, for these data, inter-occasion variability (IOV) for each chronological treatment period was tested on the absorption parameters. All these binary covariates were tested in a proportional relationship. Covariate analysis followed a forward inclusion and backward deletion step, using an OFV difference of >3.84 (P <0.05) and >10.83 (P <0.001) for statistical significance, respectively. Comparisons to values reported in the literature of simulated AUC values and the ratio of AUC values under different statuses of food intake, were also used for the selection of the covariate models for the oral suspension [6, 7, 15, 16, 19].

The final model was validated using a normalized prediction distribution error (NPDE) analysis based on 1000 simulations and stratified by formulation. Stratified bootstrap (n=100) was used to assess the model robustness and parameter precision of the final model.

3.2.3 Illustration of model findings

To illustrate the exposure differences for the three posaconazole formulations, concentration-time profiles after a single dose of 300 mg posaconazole oral suspension (fed and fasted), DR-tablet (fed and fasted), and IV, were simulated with the final model for a typical healthy individual. To evaluate the commonly used dosage regimens, simulations were performed for a typical healthy individual receiving the recommended dose for the prophylaxis of invasive fungal infections. Various commonly used dosing regimens were simulated. This included 200 mg three times daily (tid) for the oral suspension and a loading dose of 300 mg twice daily (bid) on the first day followed by a maintenance dose of 300 mg once daily (qd) for both DR-tablet and IV formulation [1, 3]. For the treatment of invasive fungal infections, the simulated recommended doses included 400 mg bid and 200 mg four times daily (qid) for the oral suspension, as well as the same dose as the recommended prophylactic dose for both DR-tablet and IV formulation [1-3]. Both fed and fasted conditions were simulated for each oral regimen to illustrate the influence of food intake on posaconazole exposure.

Stochastic simulations were performed to illustrate the distribution of the exposure at a population level. Each commonly used regimen was simulated 1000 times with IIV to predict posaconazole concentration-time profiles and the 24-h AUC (AUC_{24h}).

3.3 Results

3.3.1 Population pharmacokinetic model

A two-compartment disposition model with first-order elimination and a combined proportional and additive residual error model best described the data from all formulations. For the oral suspension and DR-tablet, the absorption profile was best described by respectively four and eight absorption transit compartment models (Fig. S1). IIV was included on F, the first-order rate constant between absorption transit compartments (k_{tr}), CL, and volume of distribution of the central compartment.

Including nonlinear CL decreased OFV significantly compared with the linear CL, but the GOF plots did not show an improvement where it would be expected. For this reason, a linear CL was retained for all formulations. Incorporating dose nonlinearity on F of the DR-tablet did not significantly improve the model (P >0.05) and therefore was not included in the model.

Food intake was found to reduce the k_{tr} of the oral suspension by 52.2% (95% confidence interval of the estimate [CI] 45.2-59.2%). Based on prior knowledge and improvement in the predicted AUC values compared to literature reports, the dose-dependent decreasing sigmoidal functions for F were incorporated for the oral suspension under fed and fasted conditions, even though no statistical significance was found in our dataset compared to a dose-independent F. In addition to the dose

dependency, F of the oral suspension depends on food intake, with higher doses being associated with a larger food effect. From these covariate functions, the typical value of F at 400 mg of the oral suspension under fed and fasted conditions could be derived to be respectively 49.2% and 10.1% and they are increased to 59.1% and 17.1% respectively at a dose of 100 mg. The F at other doses can be calculated using the nonlinear equation of F in Table 2. The typical value of F of the DR-tablet was 58.8% (CI 54.4-63.2%) under fasted condition. When fed, the typical value of F in individuals receiving the DR-tablet approached 100% and was fixed to 99.5% to avoid boundary issues.

The impact of comedication on the absorption of the DR-tablet was not statistically significant, but introducing IOV on the F and k_{tr} of the DR-tablet for the five-way crossover study that tested on each occasion coadministration of drugs known to interact with the absorption of the posaconazole oral suspension [7], significantly reduced the OFV and the IIV of F in the DR-tablet, and improved goodness-of-fit plots. This was therefore retained in the model [10]. After inclusion of IOV and the food impact as a covariate, the IIV on F was still high for both the oral suspension and DR-tablet, with a 95% distribution interval of 28.4-70.2% *versus* 4.40-21.3% for a 400 mg oral suspension under fed *versus* fasted condition, and 33.2-80.4% for the DR-tablet under fasted condition. The IOVs were slightly higher than the IIVs in F (0.401 vs. 0.290) and k_{tr} (31.5% vs. 29.9%) for the DR-tablet.

Parameter estimates of the final model are presented in Table 2 and the NONMEM control stream for the final model can be found in the supplementary material. GOF plots of the final model are included in supplemental Fig. S2 and suggest that the model described the data well for each formulation. The NPDE results shown in Supplementary Fig. S3A and S3B indicate an accurate predictive performance of the final model regarding both the structural and stochastic model for each formulation. Fig. S3C suggests a good predictive performance of concentrations below the limit of quantification, with an acceptable agreement between observed data and model-simulated median and 95% CI. Model-predicted AUC values were in reasonable agreement with the reported AUC values from literature with doses ranging from 100 mg to 400 mg (Table S2). Furthermore, the final model also demonstrated good predictive performance of the food effect on the oral suspension at a dose of 100 mg, 200 mg and 400 mg (Table S3). Bootstrap results in Table 2 indicate that the final model was robust and all model parameters were estimated with good precision.

Table 2 Pharmacokinetic parameter estimates for the final posaconazole model

Parameters	Parameter estimates (RSE%) [%shrinkage]	Bootstrap[a] median (95% CI)
Population parameter values [units]		
$F_{sus,fed} = F_{sus,max,fed} \times \left(1 - \frac{Dose}{Dose + D_{50,fed}}\right)$ $F_{sus,fasted} = \frac{F_{sus,max,fed}}{2.85} \times \left(1 - \frac{Dose}{Dose + \frac{3249 \times D_{50,fed}}{5597.4 + 5.871 \times D_{50,fed}}}\right)$		
$F_{sus,max,fed}$ [%]	63.3 (8.10)	63.8 (34.9-71.6)
$D_{50,fed}$ [mg]	1390 (60.5)	1017 (205-2217)
$F_{tab,fed}$ [%]	99.5 (fixed)	99.5 fixed
$F_{tab,fasted}$ [%]	58.8 (3.80)	58.6 (53.9-64.2)
$k_{tr,sus,fed} = k_{tr,sus,fasted} * (1-\theta_{sus,fed,ktr})$		
$k_{tr,sus,fasted}$ [h^{-1}]	2.20 (6.70)	2.2 (1.99-2.4)
$\theta_{sus,fed,ktr}$ [-]	0.522 (6.90)	0.525 (0.465-0.567)
$k_{tr,tab}$ [h^{-1}]	2.70 (5.60)	2.59 (2.44-2.72)
CL [L/h]	6.65 (2.70)	6.97 (6.65-7.18)
V_c [L]	152 (4.80)	153 (135-166)
V_P [L]	109 (4.40)	110 (98-122)
Q [L/h]	46.4 (9.10)	47.3 (40.5-55.1)
Inter-individual variability in %CV		
F_{sus} [b,c]	0.206 (25.1) [50.9]	0.210 (0.100-2.94)
F_{tab} [b,c]	0.290 (26.9) [52.1]	0.320 (0.180-0.570)
$k_{tr,sus}$	20.7 (12.3) [47.5]	20.3 (15.7-25.9)
$k_{tr,tab}$	29.9 (11.7) [46.1]	28.9 (22.2-33.8)
CL	31.3 (6.80) [7.60]	30.5 (27.2-34.3)
V_c	31.3 (10.0) [19.6]	32.7 (26.8-36.8)
Inter-occasion variability[d] in %CV		
F_{tab} [b,c]	0.401 (19.7) [67.0-76.3][e]	0.433 (0.290-0.612)
$k_{tr,tab}$	31.5 (6.20) [65.0-74.2][e]	31.8 (26.0-38.1)
Residual error		
σ_{prop}	18.8% (0.600)	18.7% (17.4%-20.3%)
σ_{addi} (mg/L)	0.0025 (4.50)	0.0023 (0.0008-0.0039)

RSE relative standard error of the estimate, CI confidence interval, F absolute oral bioavailability, Fsus,fed population value of F for the oral suspension under fed condition $F_{sus,max,fed}$ the maximum F of the oral suspension under fed condition, $D_{50,fed}$ oral suspension dose that could achieve half of the $F_{sus,max,fed}$ under fed condition, *DR-tablet* delayed-release tablet, $F_{tab,fed}$ population value of F for DR-tablet under fed condition, $F_{tab,fasted}$ population value of F for DR-tablet under fasted condition, k_{tr} first-order absorption rate constant and the rate constant between absorption transit compartments, $k_{tr,sus}$ k_{tr} of the oral suspension, $k_{tr,sus,fed}$ k_{tr} of the oral suspension under fed condition, $k_{tr,sus,fasted}$ k_{tr} of the oral suspension under fasted condition, $\theta_{sus,fed,ktr}$ proportion of food influence on k_{tr} of the oral suspension, $k_{tr,tab}$ k_{tr} of the DR-tablet regardless of food intake, *CL* clearance, V_c volume of distribution of the central compartment, V_p volume of distribution of the peripheral compartment, *Q* intercompartment clearance between central and peripheral compartments, *CV* coefficient of variation, σ_{prop} proportional residual error, σ_{addi} additive residual error

[a]Bootstrap success rate was 63% for the final model using the M3 method (n = 63 out of 100)

[b]The variability of F was added within the logit domain and was presented as the variance.

[c]A 95% distribution interval with the 2.5th and 97.5th percentiles calculated by $\left(\frac{e^{ln\left(\frac{F}{1-F}-1.96\times\sqrt{(\omega_F^2)}\right)}}{1+e^{ln\left(\frac{F}{1-F}-1.96\times\sqrt{(\omega_F^2)}\right)}}, \frac{e^{ln\left(\frac{F}{1-F}+1.96\times\sqrt{(\omega_F^2)}\right)}}{1+e^{ln\left(\frac{F}{1-F}+1.96\times\sqrt{(\omega_F^2)}\right)}}\right)$ was used to describe the inter-individual variability of F. The 95% distribution interval for 200 mg of oral suspension under fed and fasted conditions were 33.7-75.1% and 6.2-28.0%, respectively. The 95% distribution interval for 400 mg of oral suspension under fed and fasted conditions were 28.4-70.2% and 4.4-21.3%, respectively. The 95% distribution interval for the DR-tablet under fed and fasted conditions were 98.6-99.8% and 33.2-80.4%, respectively

[d]Inter-occasion variability was only incorporated in a five-way crossover study for the DR-tablet (P07764) [10]

[e]Shrinkages for the inter-occasion variability of each occasion are different and therefore were summarized as a range

3.3.2 Illustration of model findings

The distribution of F for both oral formulations under fed and fasted conditions is illustrated in Fig. 1. It can be seen that food intake increases F for both oral formulations, which is more pronounced for the suspension compared to the DR-tablet. Moreover, the overall F for the oral suspension is lower than for the DR-tablet, causing the median value for F of the oral suspension at 100 mg under fed conditions to be comparable with that of the DR-tablet under fasted condition.

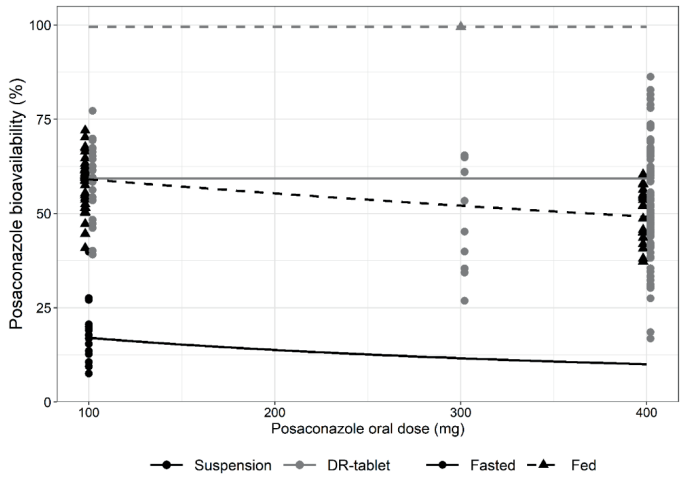

Fig. 1 Population prediction of posaconazole bioavailability (lines) and individually estimated bioavailability (symbols) *versus* dose for the oral suspension and the delayed-released tablet (DR-tablet) under fed and fasted conditions. At 100 and 400 mg symbols were placed next to each other to allow a better visual comparison

Fig. 2 illustrates exposure-time profiles in a typical healthy individual receiving a single dose of 300 mg for each formulation under fed and fasted conditions. The exposure of the oral suspension under fed conditions is similar to the exposure of the DR-tablet under fasted condition. The AUC of the oral suspension under fasted condition yields approximately one-quarter of the exposure value of the oral suspension under fed condition or DR-tablet under fasted condition, and one-sixth of the exposure of the DR-tablet under fed condition or IV.

Fig. 3 shows the simulated typical concentration-time profiles for healthy individuals over a week, for four commonly used posaconazole dosage regimens for the three posaconazole formulations. Owing to the use of loading doses, steady state is achieved after the first day for the regimen of the DR-tablet and the IV infusion, but takes about 5 days to be reached for the regimen with the oral suspension. In typical healthy individuals receiving posaconazole under fed conditions, all simulated dosing scenarios achieve C_{trough} ≥1.25 mg/L at steady state. However, under fasted conditions, the DR-tablet regimen yields a prophylactic steady-state C_{trough} ≥0.7 mg/L,

but fails to achieve treatment values of ≥1 mg/L, while all three suspension regimens even fail to achieve the prophylactic target when fasted.

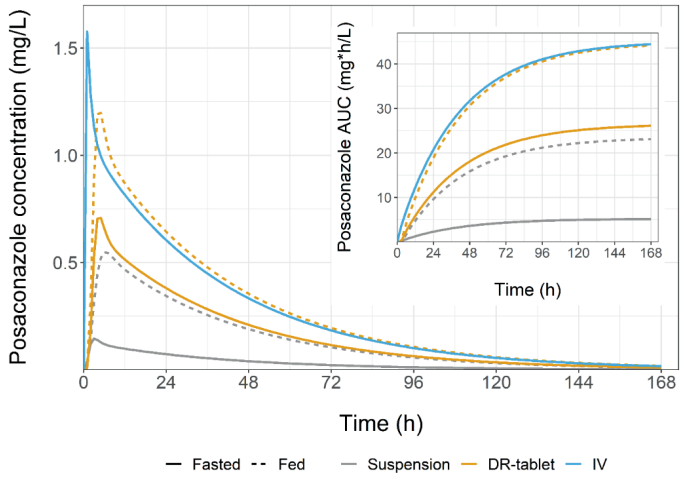

Fig. 2 Posaconazole concentration-time profiles in a typical healthy individual receiving a 300 mg single dose given as oral suspension, delayed-release tablet (DR-tablet), or intravenous infusion (IV). Profiles for oral formulations were simulated under both fed and fasted conditions. The upper right insert exhibits the area under the concentration-time curve (AUC)

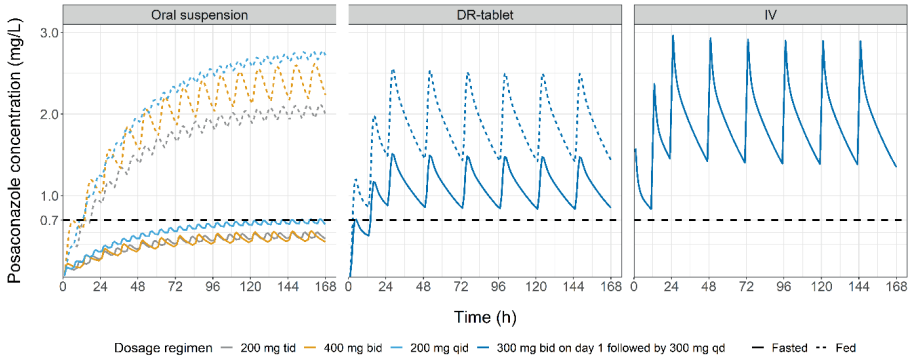

Fig. 3 Typical posaconazole concentration-time profiles in healthy volunteers receiving commonly used posaconazole doses for treatment and/or prophylaxis by oral suspension, delayed-release tablet (DR-tablet) and intravenous infusion (IV). Profiles for oral formulations were simulated under both fed and fasted conditions. The horizontal dashed line (0.7 mg/L) represents the trough concentration target for prophylaxis in patients

tid three times daily, *bid* two times daily, *qd* once daily

The simulations in Fig. 4 were performed to present the distribution of posaconazole concentration and AUC_{24h} *versus* time over one week in 1000 healthy individuals.

With food intake, both recommended prophylactic posaconazole oral regimens of 200 mg tid of the oral suspension and 300 mg bid on the first day followed by 300 mg qd thereafter of the DR-tablet, yield a C_{trough} ≥0.7 mg/L in over 90% of healthy volunteers on day 7. However, once the same dose is given fasted, only 20% of healthy volunteers receiving the oral suspension, and 65% of the population receiving the DR-tablet achieve this target. Under fed conditions, >90% of healthy volunteers receiving the three commonly used oral suspension regimens (i.e., 200 mg tid, 400 mg bid, 200 mg qid), and >80% of the population receiving the commonly used DR-tablet regimen achieve a C_{trough} ≥1.0 mg/L on day 7. The recommended IV regimen of 300 mg bid on the first day followed by 300 mg qd yields a steady-state C_{trough} ≥1.0 mg/L in over 70% of the population.

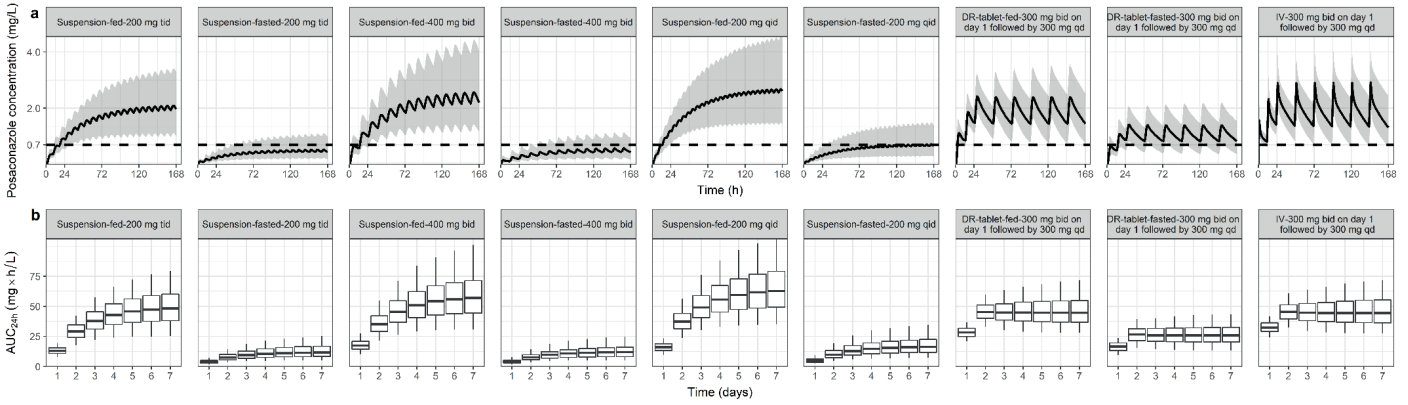

Fig. 4 Distribution of posaconazole concentration-time profiles (a) and distribution of the area under the curve per day (AUC_{24h}) (b) in 1000 simulated healthy volunteers receiving commonly prescribed posaconazole regimens for the oral suspension, delayed-release tablet (DR-tablet) and intravenous infusion (IV). Profiles for oral formulations were simulated under both fed and fasted conditions. In a, the solid lines represent the median concentration, and the shaded areas represent the 90% prediction interval for the simulated individuals and the horizontal dashed line (0.7 mg/L) represents the concentration target for prophylaxis in patients. In b, the boxes represent the 25th, 50th (median), and 75th percentiles, and whiskers represent the 5th and 95th percentiles (i.e., 90% distribution interval)

tid three times daily, *bid* two times daily, *qd* once daily

3.4 Discussion

This study integrates the quantification of the pharmacokinetics of all currently available pharmaceutical formulations of posaconazole. Furthermore, absolute F and oral absorption rate were quantified including the influence of dose and food for both oral formulations in healthy volunteers. This study is the first to directly compare these formulations and quantify the dose-dependent nonlinear F for the oral suspension under fed and fasted conditions. One of the strengths of this study is the large amount of dense data for each formulation together with the novel application of available literature data during parameter estimation and covariate selection. Additionally, the potentially confounding influence of pathological and clinical factors was circumvented by focusing on healthy individuals, which allows for better clarification of the pharmacokinetic difference among the three formulations.

Nonlinearity in posaconazole exposure with an increasing oral suspension dose is well known and attributed to solubility issues in the gastrointestinal tract, that can be partly counteracted with the coadministration of food [28, 29]. Moreover, it has been reported for healthy volunteers that the difference in posaconazole exposure between fed and fasted condition varies for different doses, which could be explained by the fact that solubility issues are less for lower doses, therefore the impact that food can have on increasing the solubility is also less [7]. The available previous knowledge, including reported quantitative differences, was included in our model with separate sigmoidal functions describing the relationship between dose and F for the fed and fasted condition. Due to the known influence of dose and food on F for the oral suspension, it was already strongly advised to divide a daily posaconazole dose over multiple smaller doses and to take the doses with a full meal to enhance oral absorption and maximize exposure [1, 3]. This advice is supported by our findings as illustrated in Fig. 3.

It should be kept in mind however, that feeding status does not have a fixed binary impact on posaconazole absorption, which our model does suggest. Differences in the impact of coadministration of various amounts of nutritional supplements, non-fat meals, and high-fat meals on F have been reported (1.35 to 2.69-fold vs. 2.68-fold vs. 4.91-fold, respectively) [6, 7, 30], with the value obtained in our study reflecting results obtained after high-fat meals. Additionally, in single-dose studies, 8 - 12 hours of fasting can be achieved, but upon repeated dosing multiple times per day, not all doses will be administered under the same fasting conditions. This may for instance explain the underprediction of exposure by our model, for which estimation of parameters under fasted conditions were based on single-dose studies, compared to the studies that report on qid and bid dosing under fasted conditions (Table S2).

For the DR-tablet, an absolute F of 54% was reported previously in literature for healthy volunteers [17], which is similar to our estimate of 58.8% under fasting conditions. Unexpectedly, we found that food intake considerably increased the F for the DR-tablet as well, with absorption being near-maximal under fed conditions, which

might be attributable to longer gastric residence time. This is in line with the finding from another population pharmacokinetic analysis in which it is concluded that DR-tablet administration with food results in similar exposure levels to IV [32]. As a result of the positive food effect, the recommended dosage regimen of DR-tablet in healthy volunteers yields a typical C_{trough} ≥1.25 mg/L under fed conditions, but fails to achieve C_{trough} ≥1 mg/L under fasted conditions (Fig. 3) [2]. Similar to the oral suspension, the U.S. Food and Drug Administration (FDA) suggests administering the posaconazole DR-tablet with food to increase the exposure, while the European Medicines Agency (EMA) proposed that the tablet may be taken with or without food [1, 3]. Based on our findings, administering the DR-tablet with food should be advocated to enhance oral absorption and ensure adequate exposure whenever possible.

Contrary to the oral suspension [7], concomitant use with an antacid, ranitidine, esomeprazole, and metoclopramide did not show a statistically significant impact on the absorption of the DR-tablet. This is in agreement with a <10% difference in AUC reported by a model-independent method [10]. The IIV in the pharmacokinetics of the oral suspension might be slightly underestimated because the 16 healthy volunteers in the crossover study P04975 were considered as separate individuals under both fasting and fed conditions. Even so, high IIV on F was found for both the oral suspension and DR-tablet, which contributes to the high variability in exposure levels in Fig. 4. Moreover, it should be noted that the pharmacokinetic properties of the DR-tablet results in this formulation being favored in the clinic and sometimes even being used in crushed form for administration through enteral tubes [31]. Results of our analysis do however have no bearing on the exposure profile of DR-table when administered this way.

First-order [33-35], absorption lag time [36], or sequential zero first-order [37, 38], were adopted by published studies to describe oral absorption of posaconazole. In our analysis, these methods did not outperform the transit compartment approach in describing the absorption profile for both oral formulations in our analysis. This discrepancy could result from the high-density data obtained during the absorption phase in our analysis, and from the healthy study population that avoids interference of pathological factors on absorption. As expected, with the acid-resistant pH-sensitive film, the DR-tablet showed a longer absorption delay *versus* the oral suspension under the fasted condition described by a mean transit time of 2.96 h *versus* 1.82 h respectively. Under the fed condition, a longer mean transit time of 3.80 h was found for the oral suspension as a result of delayed gastric emptying [7], while this was not the case for the DR-tablet.

The pharmacokinetics of posaconazole in patients have mainly been reported in separate studies for different formulations [33-40]. Trends between exposure upon administration of the different formulations as well as the impact of food, appear to be similar to what we found for healthy volunteers, but an integrated approach will be needed to quantify the extent of these differences in patients as well. To achieve this, the current analysis needs to be enriched with data from patients. Additionally, the

impact of coadministered drugs or pathological factors including (severe) mucositis and gastric motility dysfunction, are known to reduce exposure and increase IIV in the exposure of posaconazole upon oral dosing in patients [36, 41]. Direct extrapolations from our model, which is based on healthy volunteers, to patients, cannot be made, as our simulations can be expected to over-predict the exposure and under-predict the IIV that can be expected in patients. For instance, when >90% of the simulated healthy individuals achieve the prophylactic target of IFDs if the commonly used oral prophylactic regimens are administered under fed conditions, this percentage is expected to be lower in patients. More importantly, our simulation results based on healthy individuals, already indicate a risk of underexposure for preventing IFDs when using the recommended oral dosage regimens under fasted conditions. This is of particular importance considering that food intake is often not feasible in patients [42].

To achieve the reported total posaconazole AUC_{24h}/MIC target of 167-178, which is associated with the half-maximal antifungal effects for treating aspergillosis [43-45], a deduced minimum total AUC_{24h} of 22.3 mg*h/L is required, based on the susceptible clinical MIC breakpoints of *A. fumigatus* of 0.125 mg/L [2]. Our simulations show that the recommended posaconazole oral suspension therapeutic dose of 400 mg bid or 200 mg qid is adequate to reach this target at steady state under fed conditions, but not under fasted condition for which >90% or >70% of the individuals fail to achieve this target, respectively (Fig. 4). This is an urgent alert for hematological patients after receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes or hematopoietic stem cell transplant recipients who are commonly not capable of taking food and often suffer from gastrointestinal mucositis, which could lead to even lower exposure in comparison to the healthy population [36, 46]. The DR-tablet and IV formulations are only approved for prophylactic purposes by the FDA, while the EMA has approved both formulations as first-line therapy for treating (refractory) invasive aspergillosis, as well as refractory fusariosis, chromoblastomycosis, and coccidioidomycosis [47]. Based on our simulation results in healthy volunteers in Fig. 4, the recommended dosage of DR-tablet under fed condition and IV yielded an AUC_{24h} ≥22.3 mg*h/L for more than 95% of individuals at steady state. Yet, only about 66% of the simulated healthy individuals could achieve this treatment target when the DR-tablet is administered under fasted condition. For this reason, the DR-tablet should be used with caution for treating *Aspergillus* pathogen with an attenuated MIC in patients who are intolerant to food, due to the risk of suboptimal exposure.

3.5 Conclusions

This study characterized the pharmacokinetics for all three available formulations of posaconazole in a healthy population. The dose-dependent nonlinear F and difference in this function between fed and fasted conditions were quantified for the oral suspension. The pharmacokinetic superiority of the DR-tablet was demonstrated under both fed and fasted conditions compared with the oral suspension. The

impact of food on the bioavailability of the DR-tablet is larger than anticipated, which suggests that administering the DR-tablet with food should be considered to enhance absorption. Future investigations quantifying the pharmacokinetic differences between healthy individuals and patients for the three formulations are warranted.

3.6 Supplementary materials

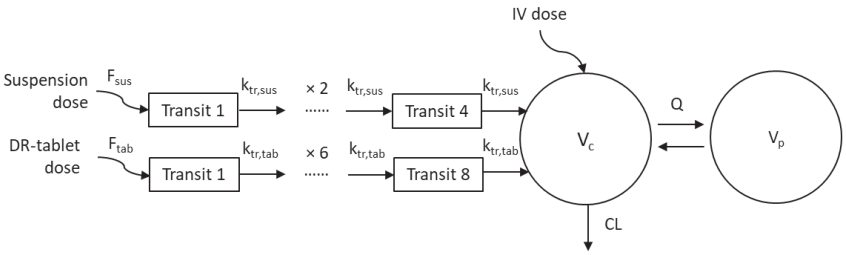

Fig. S1 Schematic representation of the integrated pharmacokinetic model for three formulations of posaconazole

DR-tablet delayed-release tablet, *IV* intravenous infusion, *F* absolute bioavailability, F_{sus} F of the oral suspension, F_{tab} F of the DR-tablet, k_{tr} first-order absorption rate constant and the rate constant between absorption transit compartments, $k_{tr,sus}$ k_{tr} of the oral suspension, $k_{tr,tab}$ k_{tr} of the delayed-release tablet, *CL* clearance, V_c the volume of distribution of the central compartment, V_p the volume of distribution of the peripheral compartment, *Q* interdepartmental clearance

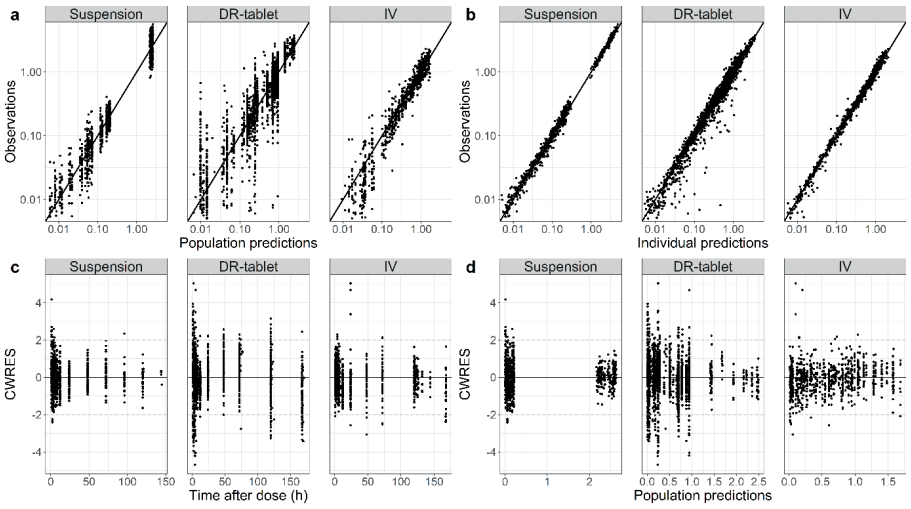

Fig S2. Goodness-of-fit plots of the final model for oral suspension, delayed-release tablet (DR-tablet) and intravenous infusion (IV), with (a) observed *versus* population predicted posaconazole concentrations, (b) observed *versus* individual predicted posaconazole concentrations, (c) conditional weighted residuals *versus* time after dose and (d) *versus* population predicted posaconazole concentrations. The solid lines in plots (a) and (b) represent the line of identity (y=x)

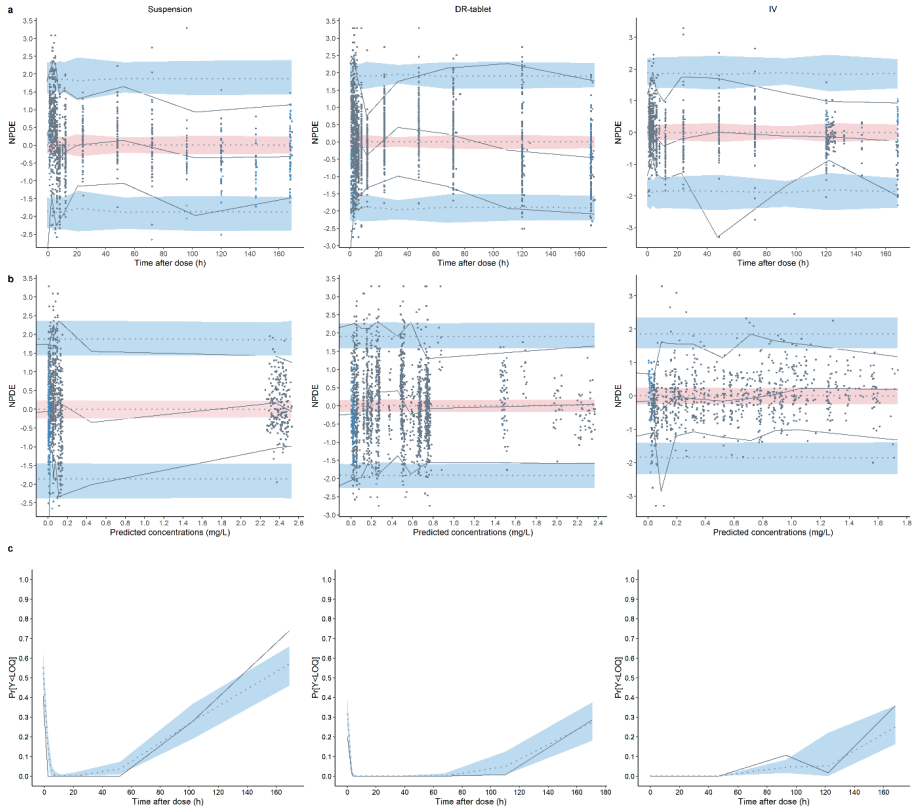

Fig. S3 Normalized prediction distribution error (NPDE) *versus* time after dose (**a**), NPDE *versus* predicted concentrations (**b**), and the probability of posaconazole concentration being below the limit of quantification (Pr[Y<LOQ]) *versus* time after dose (**c**) of the final model for oral suspension, delayed-release tablets (DR-tablet) and intravenous infusion (IV). In plot **a** and **b**, each prediction interval (95%) of simulated concentrations (n = 1000) is plotted as a colored area (blue for the 2.5th and 97.5th percentiles and pink for the median). The corresponding 2.5th, 50th, and 97.5th percentiles of the observed and predicted data are plotted as solid and dotted lines, respectively. Concentrations detected below the limit of quantification are indicated in steel blue color in the scatter plots. In **c**, lines represent the observed (solid) and median predicted (dotted) proportion below the LOQ, where the blue shaded areas represent the 95% confidence intervals based on simulated concentrations (n = 1000)

Table S1 Summary of the pharmacokinetic data included in this analysis, separated by study

Study	Merck-4975 [1]		Radboudumc [2]	Merck-7691 [3]		Merck-7764 [4]	Merck-7783 [3]			Merck-4985 [5]	Merck-6356 [6]	Radboudumc [7]
Formulation	Suspension		Suspension	Suspension	DR-tablet	DR-tablet	DR-tablet		IV	IV	IV	IV
Food intake	fasted[a]	fed[a]	fed	fed	fasted	fasted	fasted	fed	NA	NA	NA	NA
Single (SD) or multiple (MD) dose	SD	SD	MD	SD	SD	SD	SD	MD	SD	SD	SD	SD
No. of subjects	16	15	20	24	22	21	12	12	12	9	45	8
Dosage (mg)	100	100	400 bid	100	100	400	300	300 qd	300	200	50, 100, 200, 250, 300	300
Duration of sampling after the last dose (h)	168	168	12	168	168	168	168	168	168	144	168	48
No. of total concentrations	256	240	220	312	286	1304	156	178	156	179	531	80
No. of concentrations per subject, median	16	16	11	13	13	65	13	16	13	20	12	10
No. of BLOQ concentrations	62	48	0	31	45	52	13	0	4	1	43	0
Occasion(s)	1	1	1	1	1	1 - 5	1	1	1	1	1	1
Covariates	food		food	food		food, comedications[b]	food		NA	NA	NA	NA

DR-tab delayed-release tablet, *IV* intravenous infusion, *NA* not available, *bid* twice daily, *qd* once daily
[a]Fed and fasted groups cannot be distinguished based on the accessible data and were considered as different individuals in the analysis
[b]Crossover design with each subject receiving posaconazole DR-tablet four comedications at different treatment periods, including Mylanta, ranitidine, esomeprazole, and metoclopramide
[c]Participants took breakfast 1h after drug intake

Table S2 Comparison of AUC values reported in the literature based on non-compartmental analyses and AUC values predicted for the same conditions by our final model for oral suspension.

Reference	Dosing scenarios			Reported mean AUC [ng*h/mL]		Predicted typical AUC [ng*h/mL] (percentage error[a])
Author Year [2, 8, 3, 1, 9]	Regimen	Dose	Food	AUC type	values	values
Krishna et al. 2012 [1]	Single dose	100[b]	Fasted	AUC_{0-168h}	2970	2520 (15%)
		100[b]	Fed	AUC_{0-168h}	8470	8733 (%)
Merck-EMA-P07691 2014 [3]		100[b]	Fed	AUC_{0-168h}	8018	8733 (↑9%)
Courtney et al. 2004 [8]		200	Fasted	AUC_{0-72}	3553	3443 (3%)
		200	Fed	AUC_{0-72}	13885	13660 (2%)
Krishna et al. 2009 [9]		400	Fasted	AUC_{0-168h}	4280	5927 (↑38%)
		400	fed	AUC_{0-168h}	21000	29078 (↑38%)
	Multiple dose	200 qid	Fasted	AUC_{0-168h}	132000	29613 (↓78%)
		400 bid	Fasted	AUC_{0-168h}	52300	23062 (↓56%)
Bruggemann et al. 2010 [2]		400 bid[b,c]	Fed	AUC_{0-12h}	30400	29320 (↓4%)

The green color indicates a prediction accuracy with a percentage error of <50%. The red color indicates a poor prediction accuracy with a percentage error ≥50%
[a]Percentage error = ((predicted-reported)/reported)*100%
[b]Scenarios for which data were included in our analysis
[c]Posaconazole oral suspension 200 mg qd on day 1, 200 bid on day 2, 400 mg bid from day 3 to day 10
AUC the area under the concentration-time curve, *tid* three times daily, *bid* two times daily, *qd* once daily

Table S3 Comparison of the ratio in bioavailability between fed and fasted conditions reported in the literature and derived from simulations with our final model. As in our model, differences in AUC are fully driven by differences in bioavailability, AUC ratios are used as a proxy for ratios on bioavailability

Author Year	Single Dose	Reported food effect on AUC[a]	Predicted food effect on AUC[a] (percentage error[b])
Krishna *et al.* 2012 [1]	100	2.85	3.46 (↑21%)
Courtney *et al.* 2004 [8]	200	3.91	3.98 (↑2%)
Krishna *et al.* 2009 [9]	400	4.91	4.87 (↓1%)

The green color indicates a percentage error of <50%
[a]The reported ratio of F was considered as same as the ratio of AUC
[b]Percentage error = ((predicted-reported)/observed)*100%

NONMEM Control Stream for the Final Model

```
$PROBLEM posaconazole PK of 3 formulations in healthy volunteers
$INPUT ID TIME TAD DV MDV AMT ADDL II CMT RATE EVID DOSE LLOQ BLOQ HALFLOQ FORM NEWSTU STU MD OCC DENSE
FOOD DDI MYL RANT ESOM METO FOS SEX WT AGE HT BMI BSA IBW FFM
$DATA LC_Posaconazole_3formulations_20210922_M3.csv IGNORE=@
$SUB ADVAN13 TOL=9

$MODEL
COMP=(DEPOT1) ;1
COMP=(DEPOT2) ;2
COMP=(CENT) ;3
COMP=(PERI) ;4
COMP=(TRANS1) ;5 1st transit compartment sus
COMP=(TRANS2) ;6 2nd transit compartment sus
COMP=(TRANS3) ;7 3rd transit compartment sus
COMP=(TRANS5) ;8 1st transit compartment DR-tab
COMP=(TRANS6) ;9 2nd transit compartment DR-tab
COMP=(TRANS7) ;10 3rd transit compartment DR-tab
COMP=(TRANS8) ;11 4th transit compartment DR-tab
COMP=(TRANS9) ;12 5th transit compartment DR-tab
COMP=(TRANS10) ;13 6th transit compartment DR-tab
COMP=(TRANS11) ;14 7th transit compartment DR-tab
COMP=(AUC) ;15 AUC compartment

$ABBR REPLACE ETA(OCC_KTR) = ETA (,9 to 13 by 1)
$ABBR REPLACE ETA(OCC_FTAB) = ETA (,14 to 18 by 1)

$PK
FED=0
IF (FOOD.NE.0) FED=1; FOOD=1=fed, FOOD=0=fasted
; FORM=1=sus, FORM=2=DR-tab, FORM=3=iv
IF (FORM.EQ.1) KTR = THETA (1) *(1+(FED*THETA (9))) *EXP (ETA (1)); KTR-sus
IF (FORM.EQ.2.AND.NEWSTU.NE.4) KTR = THETA (2) *EXP (ETA (2)); KTR-tab
IF (FORM.EQ.2.AND.NEWSTU. EQ.4) KTR = THETA (2) *EXP (ETA (2) +ETA(OCC_KTR)); KTR-tab with IOV
CL = THETA (3) *EXP (ETA (3)); CL in all populations
V3 = THETA (4) *EXP (ETA (4))
V4 = THETA (5) *EXP (ETA (5))
Q = THETA (6) *EXP (ETA (6))

F1=0
FMAXFED = THETA(7)
FMAXFAST = FMAXFED/2.85
D50FED = THETA(10)
D50FAST = (3249*D50FED)/(5597.4+(5.871*D50FED))
IF (FORM==1.AND.FED==0) TVF1 = FMAXFAST*(1-(DOSE/(D50FAST+DOSE)))
IF (FORM==1.AND.FED==1) TVF1 = FMAXFED*(1-(DOSE/(D50FED+DOSE)))
LGTBIOS=LOG(TVF1/(1-TVF1))
LGBIOS=LGTBIOS+ETA(7)
F1=EXP(LGBIOS)/(1+EXP(LGBIOS))

F2=0
IF (FORM.EQ.2.AND.FED.EQ.0) TVF2 = THETA(8)
IF (FORM.EQ.2.AND.FED. EQ.1) TVF2 = 0.995
LGTBIOT=LOG(TVF2/(1-TVF2))
IF (FORM.EQ.2.AND.NEWSTU.NE.4) LGBIOT=LGTBIOT+ETA (8)
IF (FORM.EQ.2.AND.NEWSTU. EQ.4) LGBIOT=LGTBIOT+ETA (8) +ETA(OCC_FTAB)
F2=EXP(LGBIOT)/(1+EXP(LGBIOT))

F3=1
K34 = Q/V3
K43 = Q/V4
K30 = CL/V3
S3 = V3

$DES
DADT (1) = -KTR*A (1); SUS
DADT (2) = -KTR*A (2); TAB
DADT (3) = KTR*A (7) + KTR*A (14) - K30*A (3)- K34*A (3) + K43*A(4)
DADT (4) = K34*A (3) - K43*A (4)
DADT (5) = KTR*A (1)-KTR*A (5); SUS
DADT (6) = KTR*A (5)-KTR*A (6)
DADT (7) = KTR*A (6)-KTR*A (7)
DADT (8) = KTR*A (2)-KTR*A (8); TAB
DADT (9) = KTR*A (8)-KTR*A (9)
DADT (10) = KTR*A (9)-KTR*A (10)
DADT (11) = KTR*A (10)-KTR*A (11)
DADT (12) = KTR*A (11)-KTR*A (12)
DADT (13) = KTR*A (12)-KTR*A (13)
DADT (14) = KTR*A (13)-KTR*A (14)
DADT (15) = A (3) /V3; AUC

$ERROR
AUC=A (15)
; M3-Method
TYPE=1
IF (DV.LT.LLOQ) TYPE=2
IF (MDV==1) TYPE=0
IF (TYPE.EQ.2) DV_LOQ=LLOQ

PROP = THETA(12)*F ; proportional part
ADD = THETA(13) ; additive part
SD=SQRT(PROP**2+ADD**2)
```

```
IPRED=F
IF(COMACT==1) PREDV=IPRED
DUM=(LLOQ-IPRED)/SD
CUMD=PHI(DUM)

IF (TYPE.NE.2.OR. NPDE_MODE==1) THEN
F_FLAG=0
Y=IPRED+SD*ERR (1)
ENDIF

IF (TYPE.EQ.2.AND.NPDE_MODE==0) THEN
F_FLAG=1
Y=CUMD
MDVRES=1
ENDIF
IF (TYPE.EQ.2) DV_LOQ=LLOQ
IRES = DV-IPRED
IWRES = IRES/SD

$THETA
(0, 2.2,5) ;1 KTR-sus
(0, 2.7,5) ;2 KTR-tab
(0, 6.65) ;3 CL
(0, 152) ;4 V3 central compartment
(0, 109) ;5 V4 peripheral compartment
(0, 46.4) ;6 Q
(0, 0.633,1) ;7 F-sus-max-fed
(0, 0.588,1) ;8 F-tab
(-1, -0.522,1) ;9 FOOD proportional impact on KTR-sus
(100, 1390) ;10 D50-FED
(0.188) ;11 Proportional error
(0.0025) ;12 Additive error

$OMEGA
0.042;1 KTR-sus
0.0854;2 KTR-tab
0.0934;3 CL
0.0937;4 V3
0 FIX ;5 V4
0 FIX ;6 Q
0.206;7 F-sus
0.29;8 F-tab
$OMEGA BLOCK (1) 0.0945; KTR-IOV
$OMEGA BLOCK (1) SAME
$OMEGA BLOCK (1) SAME
$OMEGA BLOCK (1) SAME
$OMEGA BLOCK (1) SAME
$OMEGA BLOCK (1) 0.401; IOV-FTAB
$OMEGA BLOCK (1) SAME
$OMEGA BLOCK (1) SAME
$OMEGA BLOCK (1) SAME
$OMEGA BLOCK (1) SAME

$SIGMA 1 FIX

$EST METHOD=SAEM INTERACTION AUTO=1 MAX=9999 NOABORT NUMERICAL SLOW POSTHOC LAPLACIAN
$COV SLOW UNCONDITIONAL MATRIX=R PRINT=E

$TABLE ID TIME TAD DV MDV AMT ADDL II CMT RATE EVID DOSE LLOQ BLOQ HALFLOQ FORM NEWSTU STU MD OCC DENSE
FOOD DDI MYL RANT ESOM METO FOS SEX WT AGE HT BMI BSA IBW FFM PRED IPRED PREDV ETAS(1:LAST) IRES CWRES KTR
CL V3 V4 Q F1 F2 AUC NOPRINT NOAPPEND ONEHEADER
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3.7 References

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Chapter 4

Meta-PK analysis of posaconazole upon dosing of oral suspension, delayed-release tablet, and intravenous infusion in patients versus healthy volunteers: impact of clinical characteristics and race

This chapter is based upon:

Chen L, Krekels EHJ, Dong Y, Chen L, Maertens JA, Blijlevens NMA, Knibbe CAJ, Brüggemann RJ. Meta-PK analysis of posaconazole upon dosing of oral suspension, delayed-release tablet, and intravenous infusion in patients versus healthy volunteers: impact of clinical characteristics and race. Int J Antimicrob Agents. 2023 Oct 6:106995.

Abstract

Objectives We previously developed an integrated population pharmacokinetic model for posaconazole oral suspension (SUS), delayed-release tablet (DR-tablet), and intravenous (IV) infusion in healthy volunteers (HV). Here we extended that model to patients and investigated the potential impact of clinical characteristics and the Chinese race on posaconazole pharmacokinetics.

Methods 1046 concentrations from 105 prospectively studied Caucasian patients receiving either of the three formulations were pooled with 3898 concentrations from 182 HV. Clinical characteristics were tested for significance. The Chinese racial impact was assessed using 292 opportunistic samples from 80 Chinese patients receiving SUS.

Results Bioavailability of the SUS (F_{sus}) in patients decreases from 38.2% to 24.6% when the dose increases from 100 mg to 600 mg. The bioavailability of DR-tablet (F_{tab}) was 59% regardless of dose. Mucositis, diarrhea, administration through a nasogastric tube, and concomitant use of proton pump inhibitors or metoclopramide, respectively reduced F_{sus} by 61%, 36%, 44%, 48%, and 29%, putting patients with these characteristics at increased risk of inadequate exposure. Clearance decreases from 7.0 to 5.1 L/h once patient's albumin is <30 g/L. Patients showed an 84.4% larger peripheral volume of distribution (V_p) and 67.5% lower intercompartmental clearance (Q) compared to HV. No racial difference could be identified.

Conclusions Posaconazole pharmacokinetics is considerably different in patients *versus* HV, with altered F_{sus} that is also impacted by clinical covariates, a F_{tab} similar to fasted conditions in HV, and altered parameters for clearance, V_p, and Q. No evidence suggests that Chinese patients require a different dose compared to Caucasian patients.

Keywords formulation, oral bioavailability, nonlinearity, hematology patient, Chinese

4.1 Introduction

Posaconazole is widely used for preventing or treating invasive fungal diseases (IFDs). It is currently available as an oral suspension (SUS), delayed-release tablet (DR-tablet), and intravenous (IV) infusion [1, 2]. We previously performed an integrated analysis characterizing the pharmacokinetics of all three formulations in healthy volunteers (HV), but these findings cannot be directly extrapolated to patients as their physiology may be altered or impacted by concomitant treatment. Particularly in hematology patients, pathologies and concomitant treatments are anticipated to decrease posaconazole exposure, putting them at risk for breakthrough infections or therapeutic failure [3-5]. Moreover, Chinese population was reported to have a reduced clearance (CL) compared to the global population [6], but this has not yet been confirmed in clinical practice. Although exact targets remain debated, in both prophylactic and therapeutic settings higher treatment success rates were achieved in patients with higher posaconazole exposure [7, 8].

In this study, we expand the integrated population pharmacokinetic model for all three posaconazole formulations in HV to patients, by quantifying the pharmacokinetics and investigating the influence of clinical characteristics and the Chinese race.

4.2 Methods

4.2.1 Data included in the analysis

Pharmacokinetic data were pooled from two published patient studies, hereafter referred to as patient study 1 (SUS) [7] and patient study 2 (DR-tablet and IV) [9], and eight studies in HV [10], both including mainly Caucasian individuals (see Table 1). This included 1046 concentrations from 105 patients (92% were diagnosed with hematological malignancy) receiving either of the three posaconazole formulations under various dosage regimens [7, 9] and 3898 concentrations from 182 HV that were previously analyzed [10].

In addition, a total of 292 opportunistic blood measurements (>90% trough level) from 80 Chinese patients receiving posaconazole SUS were collected from the First Affiliated Hospital of Xi'an Jiaotong University between Jan 2016 to June 2018 (Table 1). For these samples, a validated liquid chromatography-tandem mass spectrometry assay was used to measure posaconazole plasma concentrations within a quantification range from 0.005 to 5.0 mg/L [11]. Information on drug prescriptions, sampling times, and covariates was retrieved from the electronic health record using a standardized template. The actual dosing time of the SUS for these Chinese patients was not reported and thus assumed to be each mealtime at 8:00, 12:00, and 19:00, starting at the first meal after the prescription.

Table 1 Summary of the pharmacokinetic data from healthy volunteers and patients[a] included in this analysis

Characteristics		SUS			DR-tablet		IV	
Population [reference]		HV [12-14]	Patients [7]		HV [13, 15]	Patients [9]	HV [13, 16-18]	Patients [9]
No. of studies		3	1 (study 1)	1	3	1 (study 2)	4	1 (study 2)
No. of subjects		75	82	80	67	19	74	21
Race		Caucasian	Caucasian [7]	Chinese	Caucasian	Caucasian	Caucasian	Caucasian
Dosage (mg)	Single dose	100	NA	NA	100, 300, 400	NA	50, 100, 200, 250, 300	NA
	Multiple dose	Day 1: 200 qd; Day 2: 200 bid; Day 3-10: 400 bid	median dose (range): prophylaxis: 200 tid (40 bid - 300 tid); treatment: 400 bid (200 tid - 400 tid)	median dose: 400 mg bid (range 100 mg bid to 300 mg tid)	300 mg bid on day 1 followed by 300 qd	Day 1: 300 bid; Day 2-12: 300 qd; Day 13: 200 qd	NA	Day 1: 300 bid; Day 2-12: 300 qd; Day 13: 200 qd
Duration of sampling after the last dose (h)	Single dose	168	NA	NA	168	NA	48 - 168	NA
	Multiple dose	12	21S	94	48	26	NA	28
No. of concentrations		1028	465	292	1924	263	946	318
No. of BQL concentrations		141 (13.7%)	35 (7.5%)	0 (0%)	110 (5.7%)	1 (0.38)	48 (5.1%)	0 (0%)
No. of concentrations per subject, median (range)		13 (11-16)	3 (1-42)	2.5 (1-18)	13 (2-65)	17 (1-28)	12 (10-20)	16 (1-26)
Available covariates		Food status	Mucositis, administration through a nasogastric tube, diarrhea, PPIs, metoclopramide, ranitidine, sex, age, weight, BMI	Diarrhea, PPIs, sex, age, weight	Food status, comedications (antacid, ranitidine, esomeprazole, metoclopramide)	Mucositis, plasma citrulline, albumin, hematocrit, sex, age, weight, BMI	NA	Sex, age, weight, BMI

SUS oral suspension, *DR-tablet* delayed-release tablet, *IV* intravenous infusion, *HV* healthy volunteer, *NA* not applicable, *BQL* below the quantification limit, *bid* twice daily, *tid* three times daily, *qd* once daily, *PPIs* proton pump inhibitors, *BMI* body mass index

[a]89% of all patients are hematology patients. The proportion of hematology patients in Caucasian patients who received posaconazole SUS [7], in Chinese patients who received posaconazole SUS, and in Caucasian patients who received crossover DR-tablet and IV [9], is 91%, 85%, and 100%, respectively.

4.2.2 Population pharmacokinetic model

The population pharmacokinetic model was developed using the nonlinear mixed-effects modeling software NONMEM 7.5.0 supported by Pirana 3.0.0, PsN 5.2.6, and Xpose 4.7.2 [19]. In patients, 3.44% of concentrations below the quantification limit were excluded.

The model structure was adapted from the HV model [10], which included a two-compartment model with respectively four and eight absorption transit compartments for SUS and DR-tablet. In patients, adjustments in the number of absorption transit compartments were tested for the DR-tablet (study 2) [9], but not for the SUS because of the sparse nature of the data (study 1) [7]. Inter-individual variability (IIV) was included on bioavailability (F), the first-order rate constant between absorption transit compartments (k_{tr}), CL, and volume of distribution of the central compartment (V_c). Different error models were assessed for each patient study to describe residual unexplained variability. Structural and stochastic model selection was based on the reduction objective function value (OFV) of >3.84 (P<0.05) for nested models being considered statistically significant, on the physiological plausibility of the parameter estimates, on the relative standard error of parameter estimates being <50%, and on the goodness-of-fit (GOF) plots stratified by formulation and population.

Concentration-nonlinearity was tested on CL using the Michaelis-Menten equation. Like HV [10], dose-nonlinearity on F was incorporated *a priori* for the SUS in patients using a sigmoidal function but with parameters reestimated to values independent of food-status, as information on food-status was missing in patient's data. Tested covariates and their distribution were respectively summarized in Table S1 and Table S2. Correlation among the continuous covariates was summarized in Fig. S1. Binary covariates including concurrent diarrhea, mucositis, administration through nasogastric tubes, and comedication of proton pump inhibitors (PPIs), metoclopramide, or ranitidine, were investigated on both k_{tr} and F of the SUS (F_{sus}). Mucositis as binary covariate and continuous citrulline levels were tested as covariates on both k_{tr} and F of the DR-tablet (F_{tab}). Albumin and hematocrit levels were available from study 2 [9] and were investigated as continuous covariates on CL, V_c, the peripheral volume of distribution (V_p), and intercompartmental clearance (Q). Hypoalbuminemia was also tested as a binary covariate with three different cut-offs at <35, <30, and <25 g/L. Demographic covariates, including sex, age, and weight, were tested on the disposition parameters. Being a patient was tested as a binary covariate on each pharmacokinetic parameter as well as an additional IIV at the end of the covariate analysis, to prevent early identification of this covariate as a surrogate for a more mechanistic covariate. If a covariate was unique to a specific study, it was exclusively evaluated within that study. The covariate analysis followed a forward inclusion and backward deletion step, using an OFV decrease of >3.84 (P <0.05) and >10.83 (P <0.001) for statistical significance, respectively. Shark plots in

Xpose 4 were used to ascertain that the statistical significance of covariate effects was driven by a sufficient number of individuals [20].

Potential pharmacokinetic differences in Chinese patients were assessed. First, the final model developed for Caucasian patients was directly extrapolated to Chinese patients to inspect the fit from (stratified) GOF-plots and normalized prediction distribution error (NPDE). Second, the distribution of individual parameter values between the Chinese patients and Caucasian patients was visually inspected for potential bias. Subsequently, the Chinese race was tested as binary covariate on all parameters. Finally, the model fit was assessed upon inclusion of a 25% CL reduction in Chinese patients, according to a previous finding in Chinese subjects [6].

The predictive performance of the final model in Caucasian patients was assessed by an NPDE analysis based on 1,000 simulations and stratified by formulation. Validation results for the HV were presented previously [10].

4.2.3 Illustration of model findings

To illustrate differences among the posaconazole formulations and the obtained covariate effects, we simulated typical concentration-time profiles of recommended dosage regimens for each formulation in hypothetical patients with different covariates. For the SUS this included 200 mg three times daily (tid) for prophylaxis of IFDs, 400 mg two times daily (bid), and 200 mg four times daily (qid) for treatment purposes. For the DR-tablet and IV, a loading dose of 300 mg bid on the first day followed by a maintenance dose of 300 mg once daily (qd) was simulated [1, 2]. Stochastic simulations incorporating the IIV were performed in 1000 virtual patients to illustrate the distribution of trough concentrations (C_{trough}) and 24-h area under the curve (AUC_{24h}) on day 1, 5, and 14.

4.3 Results

4.3.1 Population pharmacokinetic model

The same number of transit compartments from the healthy volunteers remained the best option for describing the absorption of the DR-tablet in patients (study 2) [9]. Fig. S2 shows the model structure [10] that was used to describe the pharmacokinetic data in patients and HV. A proportional and a combined residual error model were respectively applied for patient study 1 [7] and patient study 2 [9]. Parameter estimates of the final model are presented in Table 2 and the corresponding NONMEM code is provided in the supplement.

Table 2 Posaconazole pharmacokinetic parameter estimates in the final model

Population parameter value [unit]	Parameter estimate (RSE%) [%shrinkage]
$F_{sus} = F_{sus,max} \times \left(1 - \frac{Dose}{Dose + D_{50}}\right) \times (1 + \theta_{F_{sus},MUC}) \times (1 + \theta_{F_{sus},PPIs}) \times (1 + \theta_{F_{sus},NG}) \times (1 + \theta_{F_{sus},DIAR}) \times (1 + \theta_{F_{sus},METO})$	
$F_{sus,max}$ [%]	0.429 (10.5)
D_{50} [mg]	806 (fixed)
$\theta_{F_{sus},MUC}$ [-]	-0.608 (6.80)
$\theta_{F_{sus},PPIs}$ [-]	-0.484 (9.0)
$\theta_{F_{sus},NG}$ [-]	-0.440 (13.0)
$\theta_{F_{sus},DIAR}$ [-]	-0.362 (19.2)
$\theta_{F_{sus},METO}$ [-]	-0.292 (32.4)
F_{tab} [%]	0.588 (fixed)
$k_{tr,sus} = k_{tr,sus,noCOV} \times (1 + \theta_{k_{tr},sus,PPIs})$	
$k_{tr,sus,noCOV}$ [h^{-1}]	2.21 (3.30)
$\theta_{k_{tr},sus,PPIs}$ [-]	-0.857 (2.70)
$k_{tr,tab}$ [h^{-1}]	2.52 (2.40)
$CL = CL_{noCOV} \times (1 + \theta_{CL,hypoalbuminemia})$	
CL_{noCOV} [L/h]	7.03 (3.30)
$\theta_{CL,hypoalbuminemia}$ [-]	-0.276 (20.3)
V_c [L]	144 (4.70)
$V_{p,PAT} = V_{p,HV} \times (1 + \theta_{V_p,PAT})$	
$V_{p,HV}$ [L]	119 (3.10)
$\theta_{V_p,PAT}$ [-]	0.844 (29.7)
$Q_{PAT} = Q_{HV} \times (1 + \theta_{Q,PAT})$	
Q_{HV} [L/h]	50.6 (4.90)
$\theta_{Q,PAT}$ [-]	-0.675 (10.3)
Inter-individual variability in %CV	
F_{sus} [a,b]	0.285 (22.7) [43.4]
F_{tab} [a,b]	0.553 (58.4) [55.7]
$k_{tr,sus}$	20.5 (10.1) [58.3]
$k_{tr,tab}$	27.3 (11.2) [53.0]
CL	32.1 (6.10) [14.5]
V_c	38.3 (11.5) [29.6]
Residual error in %CV	
$\sigma_{prop,study1}$	47.6 (5.50) [6.90]
$\sigma_{prop,study2}$	16.2 (10.8) [4.80]
$\sigma_{addi,study2}$ (mg/L)	0.0712 (31.6) [4.80]

RSE relative standard error of the estimate, *F* absolute oral bioavailability, F_{sus} population value of F for the oral suspension $F_{sus,max}$ the maximum F_{sus}, D_{50} oral suspension dose that could achieve half of the $F_{sus,max}$, $\theta_{F_{sus},MUC}$ proportional influence of mucositis on F_{sus}, $\theta_{F_{sus},NG}$ proportional influence of using a nasogastric tube on F_{sus}, $\theta_{F_{sus},PPIs}$ proportional influence of concomitant use of proton pump inhibitors on F_{sus}, $\theta_{F_{sus},DIAR}$ proportional influence of diarrhea on F_{sus}, $\theta_{F_{sus},METO}$ proportional influence of concomitant use of metoclopramide on F_{sus}, *DR-tablet* delayed-release tablet, F_{tab} population value of F for DR-tablet, k_{tr} first-order absorption rate constant, and the rate constant between absorption transit compartments, $k_{tr,sus}$ k_{tr} of the oral suspension, $k_{tr,sus,noCOV}$ $k_{tr,sus}$ without covariate impact, $\theta_{k_{tr},sus,PPIs}$ proportional influence of concomitant use of proton pump inhibitors on $k_{tr,sus}$, $k_{tr,tab}$ k_{tr} of the DR-tablet regardless of food intake, *CL* clearance, CL_{noCOV} CL without covariate impact, $\theta_{CL,hypoalbuminemia}$ proportional influence of hypoalbuminemia on CL, V_c volume of distribution of the central compartment, V_p volume of distribution of the peripheral compartment, $V_{p,PAT}$ V_p in patients, $V_{p,HV}$ V_p in healthy volunteers, $\theta_{V_p,PAT}$ proportional influence of being a patient on V_p, *Q* intercompartment clearance between central and peripheral compartments, Q_{PAT} Q in patients, Q_{HV} Q in healthy volunteers, $\theta_{Q,PAT}$ proportional influence of being a patient on Q, *CV* coefficient of variation, $\sigma_{prop,study1}$ proportional residual error in study 1 [7], $\sigma_{prop,study2}$ proportional residual error in study 2 [9], σ_{addi} additive residual error in study 2 [9].

[a]The variability of F was added within the logit domain and is presented as the variance[b]A 95% distribution interval with the 2.5th and 97.5th percentiles calculated by $\left(\frac{e^{\ln\left(\frac{F}{1-F}-1.96\times\sqrt{\omega_F^2}\right)}}{1+e^{\ln\left(\frac{F}{1-F}-1.96\times\sqrt{\omega_F^2}\right)}}, \frac{e^{\ln\left(\frac{F}{1-F}+1.96\times\sqrt{\omega_F^2}\right)}}{1+e^{\ln\left(\frac{F}{1-F}+1.96\times\sqrt{\omega_F^2}\right)}}\right)$ was used to describe the inter-individual variability of F. The 95% distribution interval for 200 mg and 400 mg of oral suspension were 15.5-59.9% and 12.4-53.4% respectively. The 95% distribution interval for the DR-tablet is 24.9-86.0% regardless of dose

Compared with the HV, patients showed an 84.4% larger V_p and 67.5% lower Q. Yet, no significant difference in V_c and CL could be identified between patients *versus* HV. A different nonlinear F_{sus} with a lower maximum F_{sus} was identified in patients vs. HV. Using a nonlinear equation (see Table 2) it was derived that in patients the typical F_{sus} decreases from 38.2% to 24.6% with a dose increase from 100 mg to 600 mg, regardless of food-status. Additionally, mucositis, diarrhea, administration through a nasogastric tube, and concomitant use of PPIs or metoclopramide, reduced the F_{sus} proportionally by 60.8%, 36.2%, 44.0%, 48.4%, and 29.2%, respectively. PPIs were also found to reduce the k_{tr} of the SUS by 85.7%, causing a delay in peak concentrations. For the DR-tablet, F in patients was 58.8%, which is comparable to the value for HV. The typical F of the two posaconazole oral formulations under various scenarios is illustrated in Fig. 1. Incorporating nonlinear CL in patients did not improve the model significantly (P>0.05). Opposed to incorporating albumin as a continuous covariate on CL, having hypoalbuminemia as a binary covariate with an optimized cut-off at 30 g/L statistically significantly improves the fit. The estimates indicate that patients presented with hypoalbuminemia have an altered CL of 5.1 L/h compared with the CL of 7.0 L/h in those without. No significant differences in the IIV between HV and patients could be identified.

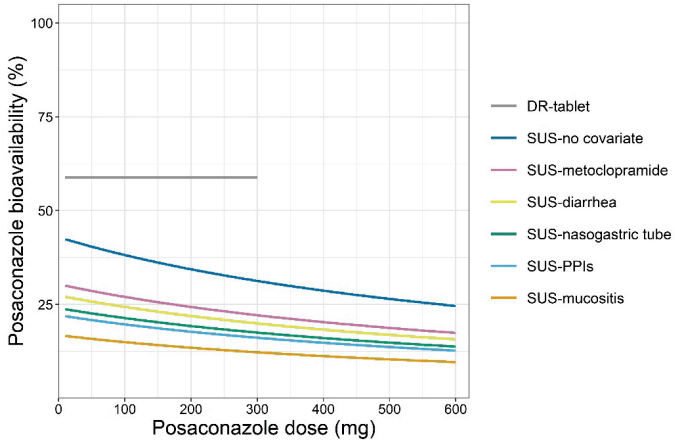

Fig. 1 Posaconazole bioavailability *versus* dose in the studied dose ranges for the delayed-released tablet (DR-tablet, no covariates were identified) and the oral suspension (SUS) in patients with and without the presence of a single covariate effect.

PPIs proton pump inhibitors

Stratified GOF-plots of the final model in supplementary Fig. S3 and Fig. S4 suggest that the model describes both healthy volunteers and Caucasian patients' data well for each formulation. The stratified NPDE results in supplementary Fig. S5 and Fig. S6 indicate an accurate predictive performance of the final model regarding both the structural and stochastic model for both population under each formulation. The GOF-plots in Fig. 2 and the NPDE results in Fig. S7 demonstrate that the pharmacokinetics in Chinese patients are not distinct from the Caucasian patients

after employing a direct extrapolation from the final model. The increased variability in Chinese patients observed in the NPDE likely results from assumptions for dose time. Moreover, the distribution of individual parameter deviations of Chinese patients *versus* Caucasian patients (Fig. S8), approximates a normal distribution with a mean of 0, as expected for a population that does not deviate from the population that was used to develop a model. Estimated deviations in parameter values for Chinese patients compared to Caucasian patients were negligible and lacked statistical significance. Incorporating 25% lower CL in our Chinese patients did not improve the model fit coupled with an increased OFV (P <0.001). Combined, all these results suggest the pharmacokinetics of posaconazole in Chinese patients to not be different from Caucasian patients.

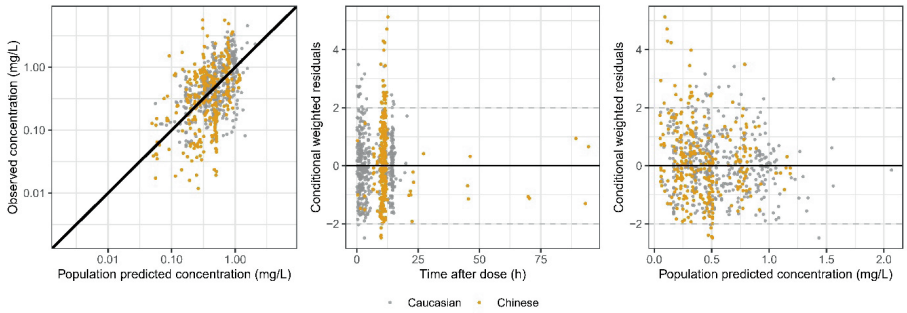

Fig. 2 Goodness-of-fit plots of the final model in the Caucasian (grey) and Chinese patients (orange) receiving the oral suspension.

4.3.2 Illustration of model findings

Since all clinical covariates retained in the final model are binary, the exposure for each clinical scenario was independently simulated and compared with the scenario where the covariate was absent. Fig. 3 presents the simulated typical concentration-time profiles in patients receiving recommended dosages of three posaconazole formulations. All covariate effects except for hypoalbuminemia, lead to a decreased exposure of the SUS, owing to a decreased F_{sus}. We report here that the standard DR-tablet regimen does not have an equivalent exposure to the IV formulation. Despite a lower daily dose compared with the SUS regimens, the DR-tablet attains a similar or higher exposure in the presence of a single covariate. Among the three SUS regimens, 200 mg qid showed the highest exposure.

Fig. 4 presents the distribution of simulated posaconazole C_{trough} and AUC_{24h} in patients on day 1, 5, and 14 in 1000 simulated patients. Without a covariate effect, the probability of target attainment (PTA) of a C_{trough} of ≥0.7 mg/L on day 14 is respectively 66%, 55%, and 90%, using the recommended prophylactic regimen

of SUS 200 mg tid, DR-tablet and IV 300 mg qd. Patients who have mucositis, diarrhea, administration through a nasogastric tube, or concomitant use of PPIs or metoclopramide receiving the prophylactic SUS regimen, achieve a PTA of C_{trough} ≥0.7 mg/L on day 14 ranging from 10%-44%. Without covariate effect, the PTA of C_{trough} ≥1.0 mg/L is respectively 65%, 31%, 28%, and 71%, using the recommended therapeutic regimen of SUS 200 mg qid and 400 mg bid, DR-tablet and IV 300 mg qd, which decreased to respectively 48%, 18%, 15%, and 51%, for the target of C_{trough} ≥1.25 mg/L.

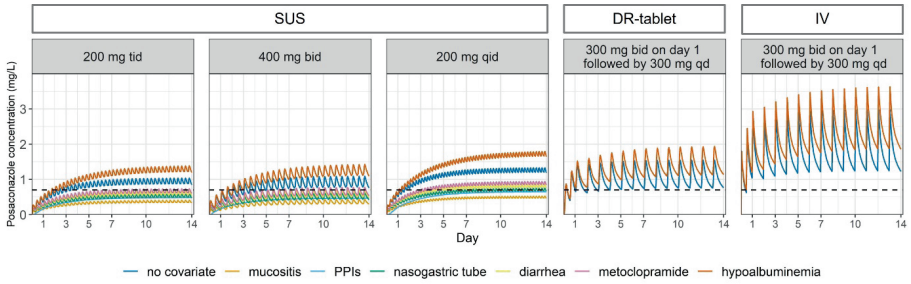

Fig. 3 Typical concentration-time profiles in patients receiving recommended posaconazole doses for oral suspension (SUS), delayed-release tablet (DR-tablet), and intravenous infusion (IV) for two weeks. Profiles were simulated under scenarios with or without single covariates with only relevant covariates included for each formulation. The horizontal dashed line (0.7 mg/L) represents the trough concentration target for prophylaxis in patients.

PPIs proton pump inhibitors, *tid* three times daily, *bid* two times daily, *qd* once daily

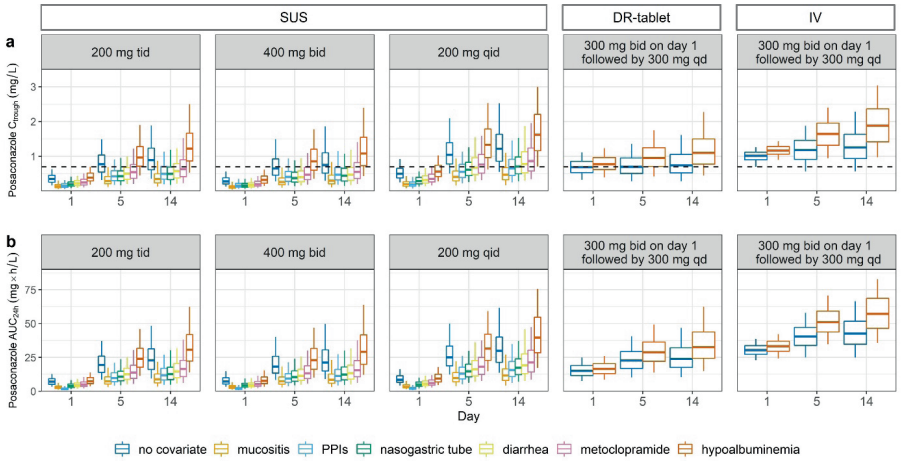

Fig. 4 Distribution of trough concentrations (**a**) and area under the curve per day (AUC_{24h}) (**b**) in 1000 simulated patients receiving recommended posaconazole regimens for the oral suspension (SUS), delayed-release tablet (DR-tablet) and intravenous infusion (IV). Profiles were simulated under scenarios with or without single covariates with only relevant covariates included for each formulation. The boxes represent the 25th, 50th (median), and 75th percentiles, and whiskers represent the 5th and 95th percentiles (i.e., 90% distribution interval). In **a**, the horizontal dashed line represents the concentration target for prophylaxis (0.7 mg/L).

tid three times daily, *bid* two times daily, *qid* four times daily dosing, *qd* once daily

4.4 Discussion

This study is the first to characterize the pharmacokinetics of all currently available formulations of posaconazole in predominantly Caucasian hematology patients in comparison to healthy volunteers. Posaconazole pharmacokinetics in patients is considerably different compared to HV, with altered F_{sus} that is also impacted by clinical covariates, a F_{tab} similar to fasted conditions in HV, and altered parameters for CL, V_p, and Q. F_{tab} is overall higher than the dose-dependent nonlinear F_{sus} and is unaffected by the tested covariates, reasserting the pharmacokinetic superiority of the DR-tablet in patients. No evidence of a racial difference could be found for Chinese patients.

Covariate analysis indicates that patients have an altered typical value of V_p and Q *versus* HV, and those with hypoalbuminemia also have an altered CL. A larger V_p was also reported in patients *versus* HV [6], possibly owing to the capillary leakage, leading to a decreased C_{trough} for all formulations along with the lower Q found in our study. Hypoalbuminemia likely acts as a surrogate for kidney disease and/or severe illness [21], which explains the lower posaconazole CL. In this case, albumin level at 30 g/L, separating normal and mild hypoalbuminemia from moderate and severe hypoalbuminemia [22], was statistically the best cut-off. Mucositis and citrulline level were included on neither F_{tab} nor the k_{tr} of the DR-tablet because it did not reach statistical significance (P<0.05) or the significance was merely driven by one patient. In the Chinese data, the high proportion of trough concentrations could barely inform the absorption, especially considering the missing accurate dosing time and food status, an external validation approach was applied to assess the influence of Chinese race. Yet with the limited data, no evidence points to a different pharmacokinetics of posaconazole between Chinese and Caucasian patients.

Compared to the data from healthy volunteers, the patient data is notably sparser during the absorption phase. Despite an average of two to six samples collected within the first six hours after dosing for each patient, this data did not provide sufficient information to support a separate IIV for the two absorption parameters (i.e., F and KTR) in patients as opposed to healthy volunteers. Consequently, all populations, including healthy individuals and patients with varying degrees of illness, shared the same variability, potentially contributing to the significant shrinkage observed in the IIV estimates for F and KTR. However, posaconazole is known for its erratic absorption, and considerable variability has been previously reported and observed in the current data. Despite the high shrinkage values, the inclusion of IIV substantially improved the model fit and was retained in the final model. To achieve the reported, yet not broadly recognized, posaconazole AUC_{24}/MIC target of 167-178 for treating aspergillosis [23-25], a deduced minimum AUC_{24} of 22.3 mg*h/L is required [26]. For this target, the recommended posaconazole SUS therapeutic doses of 400 mg bid or 200 mg qid, respectively yield a PTA of >46% or >71% at steady state in patients

without any of the clinical covariates (Fig. 4) [10]. A lower PTA is achieved when posaconazole SUS is administered to patients with one or more of the identified covariates. The standard IV dose yields an AUC_{24} ≥22.3 mg*h/L in more than 95% of all patients at steady state, while the recommended dosage of DR-tablet only yields a PTA of 81% in patients with hypoalbuminemia and 57% in those without. For this reason, both SUS and DR-tablet should be used with caution for treating Aspergillus with MIC ≥ 0.25 mg/L. Starting with a higher dose and applying therapeutic drug monitoring during the treatment can be helpful regarding the considerable variability in exposure and pathogen susceptibility.

Although lower F for both SUS and DR-tablet was demonstrated in HV under fasted *versus* fed conditions, it should be noted that both F in this study represent intermediate values between fasted and fed conditions as details on food-status were missing for patients. Yet, since 91% of the patients receiving posaconazole SUS and all patients receiving posaconazole DR-tablet suffered from hematological malignancies and they are commonly not capable of taking food, the estimated F is considered to resemble the F under fasted conditions. The higher dose and dosing frequency of the SUS regimens, can to some degree compensate for the low F_{sus}, even resulting in higher C_{trough} compared with the DR-tablet in the absence of covariates (Fig. 3). However in clinical practice, patients who receive posaconazole SUS but are without any of the clinical covariates are hardly ever encountered, which increases the risk of under-exposure.

4.5 Conclusion

Patients have altered posaconazole pharmacokinetics compared to HV which are also impacted by clinical covariates. Model performance was equal for Caucasian and Chinese patients, indicating that a different dose is not needed. For patients, the DR-tablet is superior to SUS with a higher and more stable F, but is not equivalent to IV, as commonly assumed. A considerable proportion of patients is at risk of inadequate exposure when receiving oral posaconazole at standard dose, irrespective of prophylaxis or treatment. In patients with insufficient exposure, switching to IV or increasing DR-tablet dose coupled with therapeutic drug monitoring should be considered to ensure adequate drug exposure.

4.6 Supplementary materials

Table S1 Covariates analyzed during the population pharmacokinetic analysis.

Parameters	F_{sus}	$k_{tr,sus}$	F_{tab}	$k_{tr,tab}$	CL	Q	V_c	V_p
Clinical characteristics	Covariates that could indicate gastrointestinal permeability, or could alter absorption transit time, motility, and gastrointestinal pH: mucositis, administration via nasogastric tube, diarrhea, proton pump inhibitors, metoclopramide, ranitidine		Covariates that could indicate gastrointestinal permeability: mucositis, citrulline		Covariates that could influence posaconazole distribution and clearance of posaconazole in the blood: albumin, hypoalbuminemia, hematocrit			
Population	patient vs. healthy volunteers							
Demographics	sex, age, weight, BMI							

BMI body mass index F_{sus} population value of bioavailability for the oral suspension, F_{tab} population value of bioavailability for DR-tablet, k_{tr} first-order absorption rate constant, and the rate constant between absorption transit compartments, $k_{tr,sus}$ k_{tr} of the oral suspension, *CL* clearance, V_c volume of distribution of the central compartment, V_p volume of distribution of the peripheral compartment, *Q* intercompartmental clearance between central and peripheral compartments

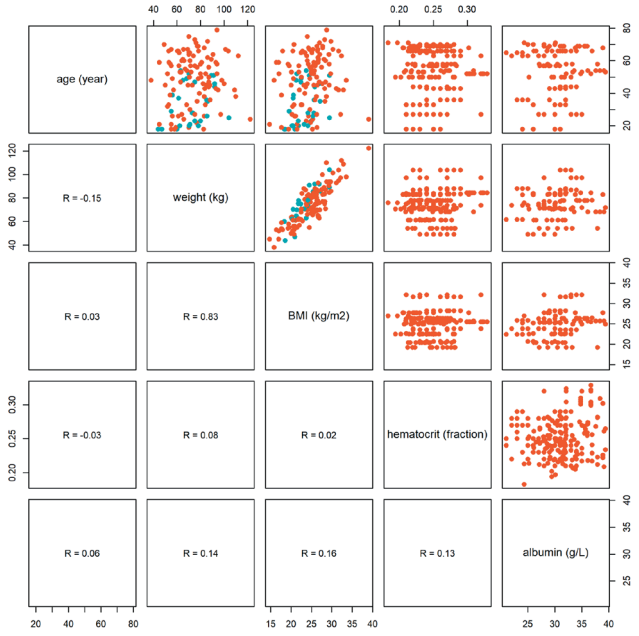

Fig. S1 Correlation between analyzed continuous covariates colored by population (blue = healthy volunteers, orange = patients).

BMI body mass index, *R* Pearson correlation coefficient

Table S2 Summary of the analyzed covariates in the pharmacokinetic analysis.

Characteristics		SUS			DR-tablet		IV	
Population [reference]		HV [12-14]	Patients [7]		HV [13, 15]	Patients [9]	HV [13, 16-18]	Patients [9]
No. of studies		3	1 (study 1)	1	3	1 (study 2)	4	1 (study 2)
No. of subjects		75	82	80	67	19	74	21
Race		Caucasian	Caucasian [7]	Chinese	Caucasian	Caucasian	Caucasian	Caucasian
Continuous covariates	age (year)	37.5 [18, 54]	50 [18, 79]	39 [12, 82]	NA	57 [27, 71]	22 [20, 37]	54 [18, 70]
	weight (kg)	74 [44, 104]	71 [38, 122]	58.5 [32.1, 90]	NA	76.1 [49.1, 104]	72.2 [61.4, 85.4]	77.3 [49.1, 97.2]
	BMI (kg/m2)	23.1 [18.3, 29.4]	24.9 [14.7, 39]	NA	NA	25.5 [19.2, 31.7]	22.5 [20.2, 25.4]	25.3 [19.2, 32.1]
	hematocrit (fraction)	NA	NA	NA	NA	0.26 [0.197, 0.303]	NA	0.247 [0.21, 0.303]
	albumin (g/L)	NA	NA	31.4 [18.9, 45]	NA	30 [24, 39.4]	NA	30 [22, 39.4]
	citrulline (µmol/L)	NA	NA	NA	NA	8.8 [5.6, 26.4]	NA	8.7 [5, 14.2]
Categorical covariates[a]	female (%)	45	43	45	NA	58	50	52
	nasogastric tube (%)	0	10	0	0	NA	0	NA
	mucositis (%)	0	39	18	0	79	0	90
	diarrhea (%)	0	40	9	0	NA	0	NA
	PPIs (%)	0	51	68	0	NA	0	NA
	ranitidine (%)	0	37	0	0	NA	0	NA
	metoclopramide (%)	0	33	0	0	NA	0	NA
	hypoalbuminemia (%)	0	NA	NA	0	63	0	67

SUS oral suspension, *DR-tablet* delayed-release tablet, *IV* intravenous infusion, *HV* healthy volunteer, *NA* not available, *BMI* body mass index, *PPIs* proton pump inhibitors

[a]All categorical covariates, with the exception of the female percentage, were time-varying covariates, and their percentage rates reflect the proportion of patients who exhibited the respective covariate scenario at least once.

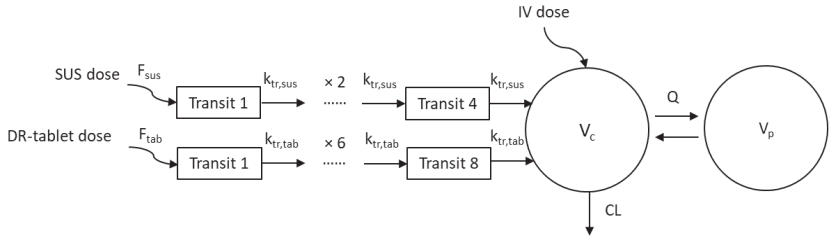

Fig. S2 Schematic representation of the integrated pharmacokinetic model for three formulations of posaconazole.

SUS oral suspension, *DR-tablet* delayed-release tablet, *IV* intravenous infusion, *F* absolute bioavailability, F_{sus} F of the oral suspension, F_{tab} F of the DR-tablet, k_{tr} first-order absorption rate constant and the rate constant between absorption transit compartments, $k_{tr,sus}$ k_{tr} of the oral suspension, $k_{tr,tab}$ k_{tr} of the delayed-release tablet, *CL* clearance, V_c the volume of distribution of the central compartment, V_p the volume of distribution of the peripheral compartment, *Q* intercompartment clearance

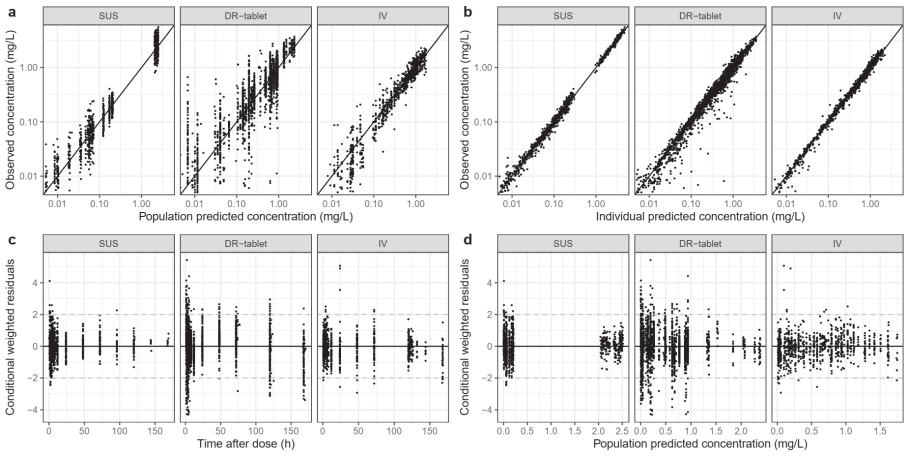

Fig. S3. Goodness-of-fit plots of the final model for oral suspension (SUS, left), delayed-release tablet (DR-tablet, middle) and intravenous infusion (IV, right) in healthy volunteers, with (a) observed *versus* population predicted posaconazole concentrations, (b) observed *versus* individual predicted posaconazole concentrations, (c) conditional weighted residuals *versus* time after dose and (d) *versus* population predicted posaconazole concentrations. The solid lines in each panel represent the line of identity (in panels (a) and (b)), and y=0 (in panels (c) and (d)). The gray dashed lines (in panels (c) and (d)) outlined the predicted 95% reference range assuming a standard normal distribution.

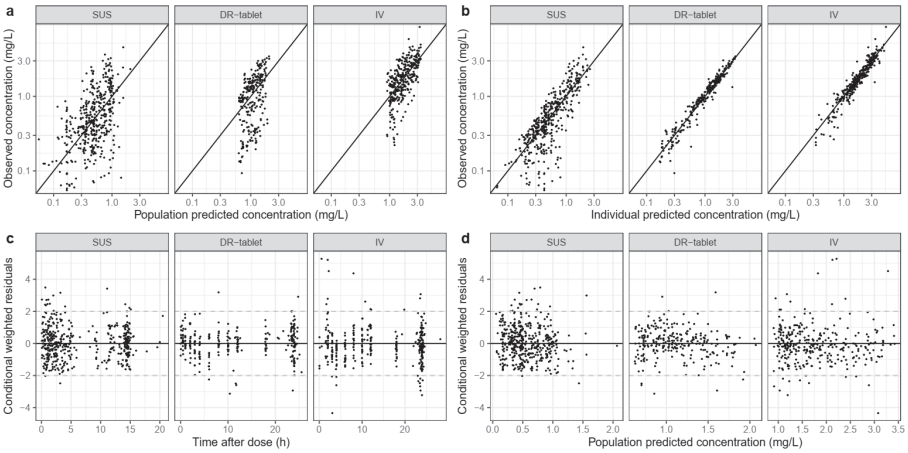

Fig. S4. Goodness-of-fit plots of the final model for oral suspension (SUS, left), delayed-release tablet (DR-tablet, middle) and intravenous infusion (IV, right) in Caucasian patients, with (a) observed *versus* population predicted posaconazole concentrations, (b) observed *versus* individual predicted posaconazole concentrations, (c) conditional weighted residuals *versus* time after dose and (d) *versus* population predicted posaconazole concentrations. The solid lines in each panel represent the line of identity (in panels (a) and (b)), and y=0 (in panels (c) and (d)). The gray dashed lines (in panels (c) and (d)) outlined the predicted 95% reference range assuming a standard normal distribution.

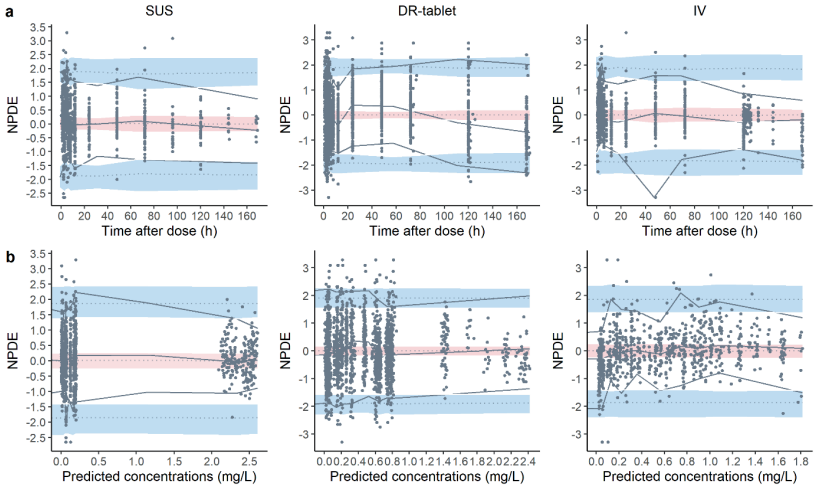

Fig. S5 Normalized prediction distribution error (NPDE) results in healthy volunteers based on the final model for oral suspension (SUS, left), delayed-release tablet (DR-tablet, middle), and intravenous infusion (IV, right), with (a) NPDE *versus* time after dose, (b) NPDE *versus* predicted concentration. In plot **a** and **b**, each 95% prediction interval of simulated concentrations (n = 1000) is plotted as a colored area (blue for the 2.5th and 97.5th percentiles and pink for the median). The corresponding 2.5th, 50th, and 97.5th percentiles of the observed and predicted data are plotted as solid and dotted lines, respectively.

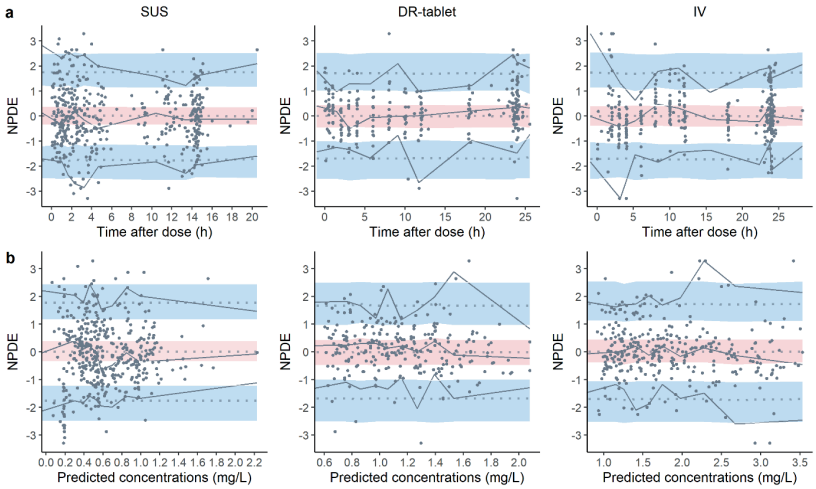

Fig. S6 Normalized prediction distribution error (NPDE) results in Caucasian patients based on the final model for oral suspension (SUS, left), delayed-release tablet (DR-tablet, middle), and intravenous infusion (IV, right), with (a) NPDE *versus* time after dose, (b) NPDE *versus* predicted concentration. In plot **a** and **b**, each 95% prediction interval of simulated concentrations (n = 1000) is plotted as a colored area (blue for the 2.5th and 97.5th percentiles and pink for the median). The corresponding 2.5th, 50th, and 97.5th percentiles of the observed and predicted data are plotted as solid and dotted lines, respectively.

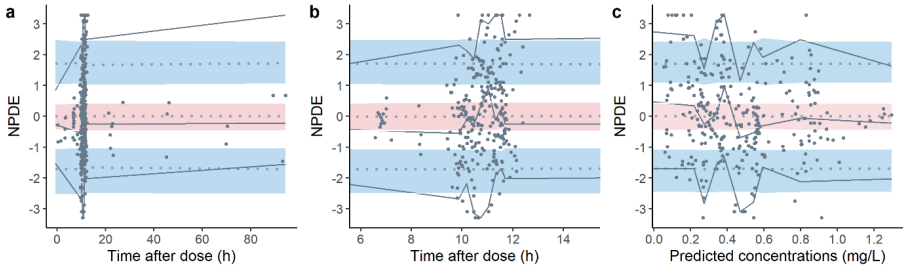

Fig. S7 Normalized prediction distribution error (NPDE) results in Chinese patients receiving the oral suspension based on the final model with (a) NPDE *versus* time after dose for all observations, (b) NPDE *versus* time after dose with the subset of observations within the most densely (>90%) sampled time interval ranging from 6 h to 15 h, (c) NPDE *versus* predicted concentration. In all plots, each 95% prediction interval of simulated concentrations (n = 1000) is plotted as a colored area (blue for the 2.5th and 97.5th percentiles and pink for the median). The corresponding 2.5th, 50th, and 97.5th percentiles of the observed and predicted data are plotted as solid and dotted lines, respectively.

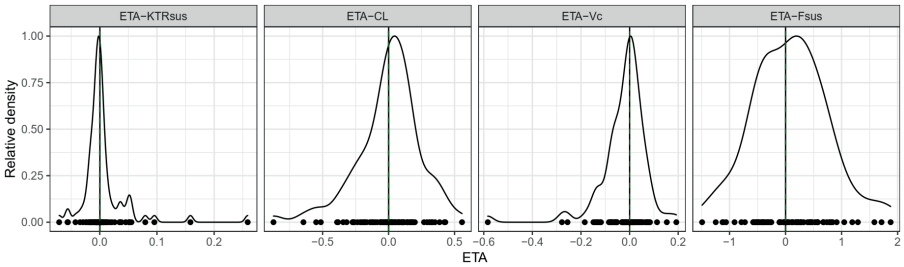

Fig. S8. Distribution of the individual parameter deviations (ETAs) of four pharmacokinetic parameters for Chinese patients receiving the oral suspension from the final estimates in Caucasian patients. MAXEVAL=0 was used in the estimation step to obtain the ETAs of the Chinese patients conditional on the Caucasian patients to achieve the best fit for the Chinese data. The solid vertical lines in plots represent the median of the ETAs (black solid) which overlap with the line x = 0 (green dashed), suggesting that the pharmacokinetic parameters in Chinese patients do not differ from those in Caucasian patients.

NONMEM Control Stream for the Final Model

```
$PROBLEM posaconazole PK of 3 formulations in healthy volunteers and patients
$INPUT ID TIME TAD DV MDV AMT ADDL II CMT RATE EVID DOSE LLOQ BLOQ FORM PAT STU MD OCC DENSE FOOD PPI MYL
RANT ESOM METO FOS NG MUC DIAR SEX AGE WT HT BMI CENTER HP ALB HPOA CITR HEMA
$DATA 367POS_HV_Patients_combineData_20220220.csv
IGNORE=@ IGNORE=(FOS==1) IGNORE=(BLOQ==1) IGNORE=(STU==11)
$SUB ADVAN13 TOL=9

$MODEL
COMP=(DEPOT1) ;1
COMP=(DEPOT2) ;2
COMP=(CENT) ;3
COMP=(PERI) ;4
COMP=(TRANS1) ;5 1st transit compartment SUS
COMP=(TRANS2) ;6 2nd transit compartment SUS
COMP=(TRANS3) ;7 3rd transit compartment SUS
COMP=(TRANS5) ;8 1st transit compartment DR-tab
COMP=(TRANS6) ;9 2nd transit compartment DR-tab
COMP=(TRANS7) ;10 3rd transit compartment DR-tab
COMP=(TRANS8) ;11 4th transit compartment DR-tab
COMP=(TRANS9) ;12 5th transit compartment DR-tab
COMP=(TRANS10) ;13 6th transit compartment DR-tab
COMP=(TRANS11) ;14 7th transit compartment DR-tab
COMP=(AUC) ;15 AUC compartment

; Define IOV for 1 healthy HV (STU==4)
OCC1 = 0
OCC2 = 0
OCC3 = 0
OCC4 = 0
OCC5 = 0

IF(STU==4.AND.OCC==1)OCC1=1
IF(STU==4.AND.OCC==2)OCC2=1
IF(STU==4.AND.OCC==3)OCC3=1
IF(STU==4.AND.OCC==4)OCC4=1
IF(STU==4.AND.OCC==5)OCC5=1

; Define IOV in STU=4 (HV)
IOV_KTRTAB =ETA(9)*OCC1+ETA(10)*OCC2+ETA(11)*OCC3 +ETA(12)*OCC4+ETA(13)*OCC5
IOV_FTAB =ETA(14)*OCC1+ETA(15)*OCC2+ETA(16)*OCC3 +ETA(17)*OCC4+ETA(18)*OCC5
```

```
$PK
FED=0
IF (FOOD/=0) FED=1; FOOD=1=fed, FOOD=0=fasted

; FORM=1=SUS, FORM=2=DR-tab, FORM=3=iv
IF(FORM==1.AND.PAT==0) KTR = THETA(1)*(1+(FED*THETA(9)))*EXP(ETA(1)) ;KTR-sus-all, KTR-PAT-unknown=KTR-HV-fast
IF(FORM==1.AND.PAT==1) KTR = THETA(1)*(1+(PPI*THETA(20)))*EXP(ETA(1)) ;KTR-sus-all, KTR-PAT-unknown=KTR-HV-fast
IF(FORM.EQ.2.AND.STU.NE.4) KTR = THETA(2)*EXP(ETA(2)) ; KTR-tab
IF(FORM.EQ.2.AND.STU.EQ.4) KTR = THETA(2)*EXP(ETA(2)+IOV_KTRTAB) ; KTR-tab

CL = THETA(3)*EXP(ETA(3))
IF(STU==9) CL = THETA(3)*(1+THETA(19)*HPOA)*EXP(ETA(3))
V3 = THETA(4)*EXP(ETA(4))
V4 = THETA(5)*(1+PAT*THETA(18))*EXP(ETA(5))
Q = THETA(6)*(1+PAT*THETA(17))*EXP(ETA(6))

F1=0
FMAXHVFED = THETA(7)
FMAXHVFAST = FMAXHVFED/2.85
D50HVFED = THETA(10)
D50HVFAST = (3249*D50HVFED)/(5597.4+(5.871*D50HVFED))
IF (FORM==1.AND.PAT==0.AND.FED==0) TVF1 = FMAXHVFAST*(1-(DOSE/(D50HVFAST+DOSE))) ;Nonlinear-F-sus-HV-fast
IF (FORM==1.AND.PAT==0.AND.FED==1) TVF1 = FMAXHVFED*(1-(DOSE/(D50HVFED+DOSE))) ;Nonlinear-F-sus-HV-fed
FMAXPAT = THETA(11)*(1+MUC*THETA(12))*(1+NG*THETA(13))*(1+PPI*THETA(14))*(1+DIAR*THETA(15))*(1+METO*THETA(16))
D50PAT = D50HVFAST
IF (FORM==1.AND.PAT==1) TVF1 = FMAXPAT*(1-(DOSE/(D50PAT+DOSE)));nonlinear-F-sus-PAT
LGTBIOS=LOG(TVF1/(1-TVF1))
LGBIOS=LGTBIOS+ETA(7); F-sus-all
F1=EXP(LGBIOS)/(1+EXP(LGBIOS))

F2=0
IF (FORM==2.AND.PAT==0.AND.FED==0) TVF2 = THETA(8) ;F-tab-HV-fasted
IF (FORM==2.AND.PAT==0.AND.FED==1) TVF2 = 0.995 ; F-tab-HV-fed
IF (FORM==2.AND.PAT==1) TVF2 = THETA(8) ;F-tab-PAT=F-tab-HV-fasted
LGTBIOT=LOG(TVF2/(1-TVF2))
IF (FORM.EQ.2.AND.STU.NE.4) LGBIOT=LGTBIOT+ETA(8)
IF (FORM.EQ.2.AND.STU.EQ.4) LGBIOT=LGTBIOT+ETA(8)+IOV_FTAB
F2=EXP(LGBIOT)/(1+EXP(LGBIOT))
F3=1

K34 = Q/V3
K43 = Q/V4
K30 = CL/V3
S3 = V3

$DES
DADT (1) = -KTR*A (1); SUS
DADT (2) = -KTR*A (2); TAB
DADT (3) = KTR*A (7) + KTR*A (14) - K30*A (3)- K34*A (3) + K43*A(4)
DADT (4) = K34*A (3) - K43*A (4)
DADT (5) = KTR*A (1)-KTR*A (5); SUS
DADT (6) = KTR*A (5)-KTR*A (6)
DADT (7) = KTR*A (6)-KTR*A (7)
DADT (8) = KTR*A (2)-KTR*A (8); TAB
DADT (9) = KTR*A (8)-KTR*A (9)
DADT (10) = KTR*A (9)-KTR*A (10)
DADT (11) = KTR*A (10)-KTR*A (11)
DADT (12) = KTR*A (11)-KTR*A (12)
DADT (13) = KTR*A (12)-KTR*A (13)
DADT (14) = KTR*A (13)-KTR*A (14)
DADT (15) = A (3) /V3; AUC

$ERROR
IPRED = 0.00001
IF(F.GT.0) IPRED = F
IF(PAT==0) Y = IPRED * (1 + EPS(1))+ EPS(2)
IF(STU==9) Y = IPRED * (1 + EPS(3))+ EPS(4)
IF(STU==10) Y = IPRED * (1 + EPS(5))+ EPS(6)

$THETA
(0, 2.29,5) ;1 KTR-sus
(0, 2.75,5) ;2 KTR-tab
(0, 7.25) ;3 CL
(0, 153) ;4 V3
(0, 119) ;5 V4
```

```
(0, 56.6) ;6 Q
(0.633) FIX ;7 F-sus-max-HV-fed
(0.588) FIX ;8 F-tab-HV-fast
(-0.522) FIX ;9 FOOD effect on KTR-sus
(1390) FIX ;10 D50-HV-fed
(0, 0.441,1) ;11 F-sus-max-PAT
(-1, -0.607) ;12 MUConFMAXPAT
(-1, -0.442) ;13 NGonFMAXPAT
(-1, -0.482) ;14 PPIonFMAXPAT
(-1, -0.362) ;15 DIARonFMAXPAT
(-1, -0.293) ;16 METOonFMAXPAT
(-1, -0.714) ;17 PATonQ
(-1, 0.837) ;18 PATonV4
(-1, -0.281) ;19 HPOAonCL-23RadHM
(-1, -0.861) ;20 PPIonKTRSUSPAT

$OMEGA
0.0344 ; 1 KTR-sus
 0.112 ; 2 KTR-tab
 0.0925 ; 3 CL
 0.133 ; 4 V3
 0 FIX ; 5 V4
 0 FIX ; 6 Q
 0.283 ; 7 F-sus
 0.647 ; 8 F-tab
$OMEGA BLOCK(1) 0.0945 FIX ;9 HV-IOV-KTRTAB
 $OMEGA BLOCK(1) 0.0945 FIX
 $OMEGA BLOCK(1) 0.0945 FIX
 $OMEGA BLOCK(1) 0.0945 FIX
 $OMEGA BLOCK(1) 0.0945 FIX
$OMEGA BLOCK(1) 0.401 FIX ;14 IOV-HV-FTAB
 $OMEGA BLOCK(1) 0.401 FIX
 $OMEGA BLOCK(1) 0.401 FIX
 $OMEGA BLOCK(1) 0.401 FIX
 $OMEGA BLOCK(1) 0.401 FIX

$SIGMA
0.0718 ; proERR-HV
 0.0025 ; addiERR-HV
 0.0261 ; proERR-RadHM
 0.00497 ; addiERR-RadHM
 0.205 ; proERR-AUSP
 0 FIX ; addiERR-AUSP
$EST PRINT=5 MAX=9999 METHOD=1 NSIG=2 SIGL=6 INTERACTION POSTHOC NOABORT MSFO=mfi
$COV PRINT=E

$TABLE ID TIME TAD DV MDV AMT ADDL II CMT RATE EVID DOSE LLOQ BLOQ FORM PAT STU MD OCC DENSE FOOD PPI MYL
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CWRES KTR CL V3 V4 Q F1 F2 NOAPPEND NOPRINT ONEHEADER
```

4.7 References

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Chapter 5

Total bodyweight and sex both drive pharmacokinetic variability of fluconazole in obese adults

This chapter is based upon:

Chen L, van Rhee KP*, Wasmann RE, Krekels EHJ, Wiezer MJ, van Dongen EPA, Verweij PE, van der Linden PD, Brüggemann RJ, Knibbe CAJ. Total bodyweight and sex both drive pharmacokinetic variability of fluconazole in obese adults. J Antimicrob Chemother. 2022 Jul 28;77(8):2217-2226.

Abstract

Background Fluconazole is commonly used to treat or prevent fungal infections. It is typically used orally but in critical situations, IV administration is needed. Obesity may influence the pharmacokinetics and therapeutic efficacy of a drug. In this study, we aim to assess the impact of obesity on fluconazole pharmacokinetics given orally or IV to guide dose adjustments for the obese population.

Methods We performed a prospective pharmacokinetic study with intensive sampling in obese subjects undergoing bariatric surgery (n=17, BMI≥35 kg/m^2) and non-obese healthy controls (n=8, 18.5≤BMI<30.0 kg/m^2). Participants received a semi-simultaneous oral dose of 400 mg fluconazole capsules, followed after 2 h by 400 mg IV. Population pharmacokinetic modelling and simulation were performed using NONMEM 7.3.

Results A total of 421 fluconazole concentrations in 25 participants (total bodyweight 61.0–174 kg) until 48 h after dosing were obtained. An estimated bioavailability of 87.5% was found for both obese and non-obese subjects, with a 95% distribution interval of 43.9%–98.4%. With increasing total bodyweight, both higher CL and V_d were found. Sex also significantly impacted V_d, being 27% larger in male compared with female participants.

Conclusions In our population of obese but otherwise healthy individuals, obesity clearly alters the pharmacokinetics of fluconazole, which puts severely obese adults, particularly if male, at risk of suboptimal exposure, for which adjusted doses are proposed.

Keywords fluconazole, obese, pharmacokinetics

5.1 Introduction

The prevalence of obesity (BMI≥30 kg/m^2) has nearly tripled over the past 50 years.[1, 2] Obese individuals often have an increased risk to develop infections, including fungal infections.[3-5] Obesity is known to influence the pharmacokinetics for many drugs and is associated with underdosing of antimicrobials, which may negatively impact clinical outcomes.[5-7]

Fluconazole is a widely used antifungal agent to prevent and treat *Candida* infections, including invasive candidiasis, and superficial infections such as oropharyngeal candidiasis, oesophageal candidiasis, candiduria and vaginal candidiasis. Low fluconazole exposure is associated with increased mortality.[8, 9] A threshold of $fAUC_{24\,h}$/MIC>100 is recommended to treat invasive candidiasis.[10-12] Due to low plasma protein binding (11%–12%), this can be translated to $AUC_{24\,h}$>200 mg·h/L for the *Candida* clinical breakpoint against fluconazole with MIC equal to 2 mg/L.[10]

Fluconazole is available for IV use and as capsules, suspension or tablets for oral administration. In non-obese subjects, the oral bioavailability (F) was reported to be over 90%, but this has not been studied in the obese population.[10] As it is reported that obesity is associated with increased gut permeability and accelerated gastric emptying, it is possible that obesity could influence the oral absorption of fluconazole.[7] Moreover, with fluconazole being primarily cleared renally, its CL could be affected by obesity, which is associated with increased renal flow.[7]

A dedicated study on the impact of obesity on the pharmacokinetics of fluconazole, in the absence of other potentially confounding patient characteristics, is lacking. This study characterizes the pharmacokinetics, including the oral F and absorption rate of the capsule formulation, in healthy non-obese and otherwise healthy morbidly obese adults. The results are used to derive model-based dosing recommendations for this special population.

5.2 Methods

5.2.1 Study population

Obese adults with BMI>35 kg/m^2 undergoing laparoscopic gastric bypass surgery or sleeve gastrectomy at the St. Antonius Hospital (Nieuwegein, The Netherlands) and non-obese healthy volunteers (BMI=18.5–30.0 kg/m^2) from the Radboud University Medical Center (Nijmegen, The Netherlands), were included. Participants were eligible for inclusion if they were aged 18–65 years. Participants were excluded if they were allergic to fluconazole or other azoles, pregnant or breastfeeding, taking medication with a known interaction with fluconazole, diagnosed with renal or hepatic dysfunctions, or had a history of long QT syndrome, or drug or alcohol abuse. Written informed consent was obtained before inclusion. This study was approved by the Dutch Medical Research Ethics Committees United (NL66611.100.18) and was

conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines (ClinicalTrials.gov identifier: NCT04122560).

5.2.2 Study design

Participants received a semi-simultaneous oral dose of 400 mg fluconazole as capsules, followed 2 h later by 400 mg IV infusion over approximately 20 min. Eight blood samples were collected after oral administration and nine samples were collected after IV administration up to 48 h after the oral dose, or until discharge for obese participants. Blood samples were collected in heparin tubes, centrifuged at 1900 g for 5 min and stored at −80°C until analysis.

In all individuals, 24 h urine and serum creatinine were collected on the day of study and glomerular filtration rate (GFR) was calculated.[13] Additionally, estimated GFR values were calculated using the 4-variable Modification of Diet in Renal Disease (MDRD),[14] the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[15] and the conventional Cockcroft–Gault either calculated with total bodyweight (TBW) or with lean bodyweight (LBW).[16, 17] MDRD and CKD-EPI were de-indexed for body surface area (BSA) by multiplying the conventional values (in mL/min/1.73 m^2) by BSA/1.73.[18]

5.2.3 Analytical assay

Fluconazole plasma concentrations were measured by a validated assay using LC coupled with tandem MS. Plasma samples were treated with protein precipitation procedures. The lower limit of detection (LOD) was 0.005 mg/L and the lower limit of quantification (LLOQ) and upper limit of quantification were 0.25 and 30.2 mg/L, respectively. The intraday and interday variability were 2.8% and 1.5%, respectively. The assay was externally validated by an international proficiency testing programme. [19, 20]

5.2.4 Population pharmacokinetic model

The population pharmacokinetic model was developed using the non-linear mixed-effects modelling software NONMEM version 7.3.0 (ICON Development Solutions, Hanover, MD, USA) supported by Perl-speaks-NONMEM (version 4.2.0) with the Pirana interface (version 2.9.0, Certara USA, Inc., Princeton, USA).[21] Data pre-processing and visualization were performed with R 4.0.3 and RStudio 1.3.959. The first-order conditional estimation method with interaction was used for all model runs.

For concentrations below the LOD (17 samples, 4.0%), half the LOD (0.0025 mg/L) was imputed. When consecutive samples were below the LOD during the absorption phase, only the last concentration was imputed and the first was omitted. Concentrations between LOD and LLOQ (six samples, 1.4%) were included in the analysis as reported by the lab.

Model development consisted of: (1) selection of the structural model, including disposition and absorption model structures; (2) selection of the statistical error model including inter-individual variability (IIV) and residual unexplained variability (RUV); and (3) covariates analysis. One- and two-compartment disposition models with linear elimination were tested. Tested approaches to describe oral absorption included first-order absorption (with and without absorption lag time), transit compartment models,[22, 23] mixed first-order and zero-order absorption[24, 25] and a Weibull function.[25] Since peak concentrations were not discernible within 2 h for most individuals, a simulation and re-estimation approach was performed to confirm the identifiability of F, which was then included with a logit function. Proportional, additive and combined additive and proportional error models were assessed for RUV. Covariance between model parameters was assessed and included in the model if correlation coefficients were >0.8.

Model selection was based on the difference in objective function value (OFV, −2 log-likelihood), on the relative standard error of parameter estimates being <50%, physiological plausibility of the parameter estimates, and basic goodness-of-fit (GOF) plots. Particular attention was paid to unbiased description in the oral absorption phase.

Potential covariates were selected based on correlations between empirical Bayes estimates and the covariates in the base model. Tested covariates include sex, age, obesity (as a binary factor), TBW, BMI, BSA, LBW,[26] ideal bodyweight[27] and adjusted bodyweight.[28] The equations for the calculation of the different body size measures can be found in Table S1, available as Supplementary data at *JAC* Online. As fluconazole is mainly renally cleared, kidney function-related measures were tested as covariates on CL. Equations for the calculation of these kidney function indices can be found in Table S2. Continuous covariates were tested with linear and power functions centralized for a typical individual of 70 kg for TBW or the median value for the covariate in the dataset. Binary covariates were incorporated with a proportional relationship. Covariate analysis followed a forward inclusion and backward deletion step, with the inclusion criteria of an OFV difference of >3.84 and >6.64, respectively.

The final model was validated using a jackknife analysis and a normalized prediction distribution error (NPDE) analysis based on 1000 simulations. Parameter precision was assessed using the sampling importance resampling method.[29]

5.2.5 Model-based dosing evaluation and optimization

Stochastic simulations using the final model were performed to illustrate the influence of covariates on fluconazole exposure, to evaluate the currently recommended dosing, and to provide guidance on optimized dosing. Male and female representatives with TBWs of 60, 100, 130 and 170 kg were simulated 1000 times with IIV to predict fluconazole concentration–time profiles and the $AUC_{24\,h}$.

For the treatment of invasive fungal infections, a dose of 800 mg on Day 1 followed by a maintenance dose of 400 mg once daily was evaluated.[30] Other loading (Day 1)/maintenance oral dosing regimens that were evaluated included 400/200 or 200/100 mg, typically used for treating oropharyngeal or oesophageal candidiasis, and 150 mg every third day for a total of three doses (Days 1, 4 and 7) in the first week, and 150 mg weekly for recurrent vaginal candidiasis.[30, 31] An $AUC_{24\ h}$ of >200 mg·h/L was selected as it is a target for the empirical treatment of invasive candidiasis that is not suspected to be located in the brain.[10] An $AUC_{24\ h}$ of >400 mg·h/L was selected as it is a target for *Candida* meningitis or encephalitis.[32-34] $AUC_{24\ h}$ on the first day of treatment and at steady state was used to assess the dosing regimen, aiming for >90% PTA. When PTA for the target of $AUC_{24\ h}$ >400 mg·h/L was not achieved, higher doses up to 1600 mg daily were explored.[35]

5.3 Results

5.3.1 Data

In total, 421 fluconazole concentrations from 25 Caucasian subjects (48% female), of which 17 were obese and 8 non-obese, with a TBW ranging from 61.0 to 174 kg, were included for pharmacokinetic analysis. One obese subject discontinued the study because of fluconazole extravasation during infusion (swelling disappeared within 24 h and no other abnormality was noted), of which concentrations measured upon oral dosing were included in the analysis. Subject details are presented in Table 1. All non-obese subjects and one obese subject had concentrations obtained until 48 h after the first dose; the remaining obese patients had observations up to 24 h. Figure 1 shows the obtained fluconazole concentration–time profiles.

Table 1. Patient and data characteristics of the obese and non-obese subjects included in the pharmacokinetic analysis

Characteristic	Obese	Non-obese
No. of subjects	17	8
Sex, *n* (%)		
Male	8 (47)	5 (63)
Female	9 (53)	3 (37)
Demographics, median (range)		
Age, years	44 (25–62)	35 (23–60)
TBW, kg	148 (106–174)	77.2 (61.0–93.5)
BMI, kg/m^2	44.1 (37.6–57.2)	23.7 (19.0–26.9)
BSA, m^2	2.54 (2.11–2.82)	1.95 (1.69–2.19)
LBW, kg	75.0 (53.8–88.7)	60.0 (40.2–69.4)
Ideal bodyweight, kg	72.3 (55.1–83.1)	73.4 (58.7–81.3)
Adjusted bodyweight, kg	101 (76.6–114)	75.8 (60.2–85.9)
Renal function measures, median (range)		
Serum creatinine, µmol/L	75.0 (54.0–89.0)	78.5 (70.0–91.0)
GFR, mL/min[a]	144 (109–187)	141 (86.7–164)

Characteristic	Obese	Non-obese
Estimated GFR		
CKD-EPI, mL/min/1.73 m^2	143 (108–175)	106 (83.1–145)
De-indexed CKD-EPI, mL/min[b]	94.9 (79.7–120)	94.5 (79.0–120)
MDRD, mL/min/1.73 m^2	133 (102–178)	101 (77.7–147)
De-indexed MDRD, mL/min[b]	94.0 (74.0–116)	90.0 (76.0–122)
Cockcroft–Gault with TBW, mL/min	222 (143–290)	108 (74.2–161)
Cockcroft–Gault with LBW, mL/min	105 (72.6–143)	76.1 (51.3–126)
Sampling profile		
No. of samples	277	144
No. of samples/subject, median (range)	16.3 (8–18)	18.0 (18–18)

[a]GFR was calculated based on 24 h urine.[13]
[b]De-indexed for BSA by multiplying the conventional values (in mL/min/1.73 m^2) by BSA/1.73.

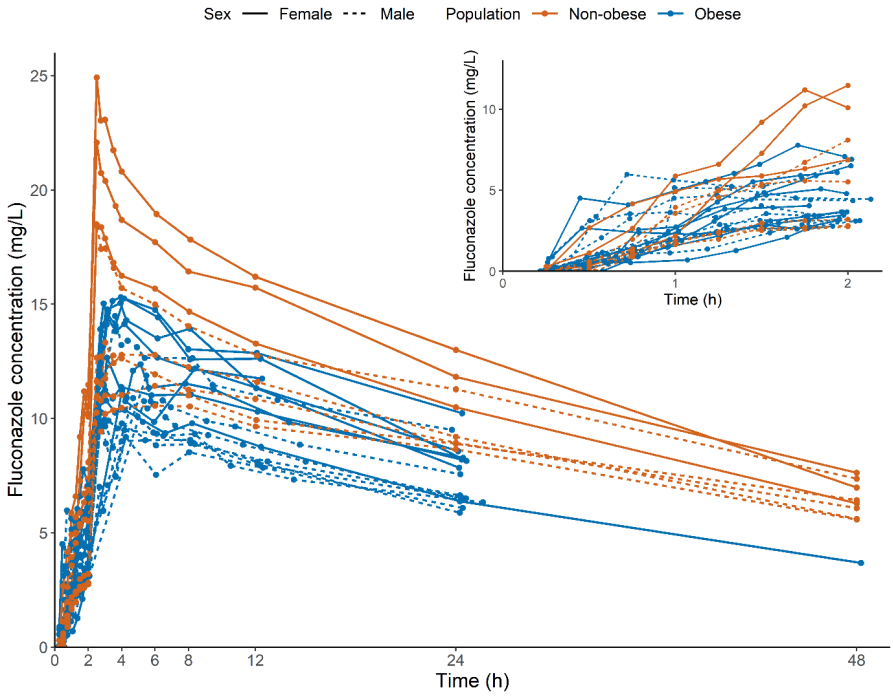

Figure 1. Individual concentration–time profiles of fluconazole for non-obese healthy subjects (*n*=8, orange) and obese but otherwise healthy subjects (*n*=17, blue). The upper right insert zooms in on the concentration–time profile in the first 2 h after oral dosing before IV administration.

5.3.2 Population pharmacokinetic model

Three absorption transit compartments connected by a one-compartment disposition model with first-order elimination and a combined proportional and additive residual error model best described the data.[22] Covariance values between parameters

were all lower than 0.8. IIV was included on F, V_d and the first-order rate constant between absorption transit compartments. No statistically significant influence of obesity or body size descriptors were found on F, therefore in the final model, the same F of 87.5% was estimated for obese and non-obese groups. IIV was relatively high, described as a 95% distribution interval of 43.9%–98.4%. Parameter estimates of the final model are presented in Table 2.

TBW in a power function in combination with sex presented a similar potential to describe IIV on V_d as LBW in a power function, yielding an OFV reduction of 45.1 versus 44.8 and a reduction of IIV on V_d from 25.2% to 6.80% versus 6.70%, respectively, with no discernible difference in GOF plots. The covariate function based on TBW and sex was included in the final model, as these are more readily available in clinical practice. Incorporating TBW on CL using a power function further improved the GOF plots and dropped the OFV by 17.7 points (P<0.001). Figure 2 illustrates the influence of TBW and sex on the V_d, and TBW on CL from the final model. Introducing kidney function indices or other demographics did not further improve the model.

Table 2. Pharmacokinetic parameter estimates for the final model

Parameter	Estimated values (RSE %) [95% CI]
$F = \frac{e^{ln\left(\frac{\theta_F}{1-\theta_F}\right)}}{1+e^{ln\left(\frac{\theta_F}{1-\theta_F}\right)}}$	
θ_F (%)	87.5 (7.70) [77.9–96.2]
k_{tr} (h^{-1})	2.69 (10.5) [2.30–3.22]
$CL = CL_{70\ kg} \times (\frac{TBW}{70})^{\theta_{TBW,CL}}$	
$CL_{70\ kg}$ (L/h)	0.908 (3.00) [0.868–0.945]
$\theta_{TBW,CL}$	0.390 (20.4) [0.214–0.532]
$V_{d,female} = V_{d,70\ kg} \times (\frac{TBW}{70})^{\theta_{TBW,V_d}}$	
$V_{d,male} = V_{d,70\ kg} \times (\frac{TBW}{70})^{\theta_{TBW,V_d}} \times (1+\theta_{sex})$	
$V_{d,70\ kg}$ (L)	38.5 (2.50) [36.6–40.6]
θ_{TBW,V_d}	0.567 (10.6) [0.474–0.679]
θ_{sex}	0.269 (21.0) [0.177–0.364]
IIV in coefficient of variation (%) (RSE%)	
k_{tr}	45.9 (14.0) [32.9–57.9]
V_d	7.26 (23.8) [4.42–10.2]
θ_F[a]	158 (25.7) [79.9–320]
Residual error in variance (RSE%)	
σ_{prop}	0.0033 (33.0) [0.00163–0.00522]
σ_{addi} (mg/L)	0.266 (30.5) [0.180–0.397]

RSE, relative standard error; CI, CI obtained in the sampling importance resampling procedure; θF, population mean value of F; k_{tr}, first-order rate constant between absorption transit compartments; $CL_{70\ kg}$, the population mean value of CL for a subject with a weight of 70 kg; $\theta_{TBW,CL}$, exponent in the exponential covariate relationships between TBW and CL; $V_{d,female}$, V_d for female subjects; $V_{d,male}$, V_d for male subjects; $V_{d,70\ kg}$ the population mean value of the V_d for a subject with the weight of 70 kg; $\theta_{TBW,Vd}$, exponent in the exponential covariate relationships between TBW and V_d; θ_{sex}, proportional increase in V_d for male compared with female subjects; σ_{prop}, proportional residual error; σ_{addi}, additive residual error.

[a]Due to logit transformation, IIV of F could be described as 95% distribution interval with the 2.5th and 97.5th percentiles calculated by $\left(\frac{e^{ln\left(\frac{\theta_F}{1-\theta_F}-1.96\times\sqrt{\omega_F^2}\right)}}{1+e^{ln\left(\frac{\theta_F}{1-\theta_F}-1.96\times\sqrt{\omega_F^2}\right)}}, \frac{e^{ln\left(\frac{\theta_F}{1-\theta_F}+1.96\times\sqrt{\omega_F^2}\right)}}{1+e^{ln\left(\frac{\theta_F}{1-\theta_F}+1.96\times\sqrt{\omega_F^2}\right)}}\right)$, i.e. 43.9% and 98.4%.

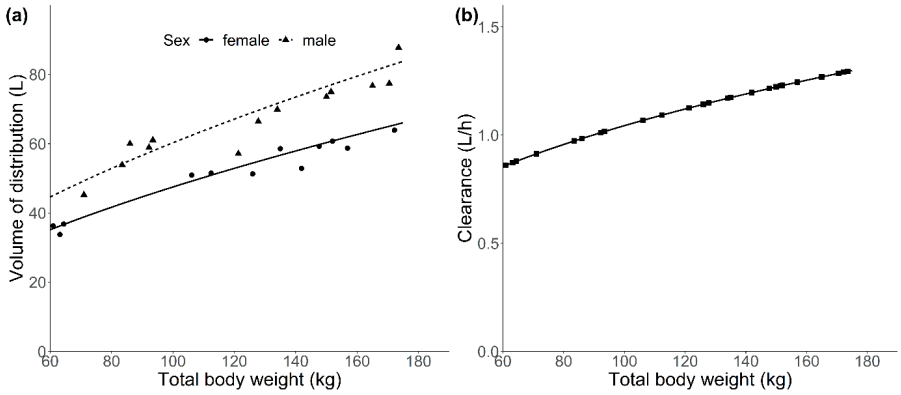

Figure 2. Individual empirical Bayes estimates (filled circles, filled triangles and filled squares) for the V_d (a) and CL (b) versus TBW from the final model. Lines represent the model-predicted relationships between the V_d and CL versus TBW.

GOF plots indicate good descriptive performance of the final model and are presented in Figure S1. The jackknife results show that exclusion of none of the individuals caused a >10% change in pharmacokinetic parameter estimates, indicating an absence of influential individuals. The NPDE results, shown in Figure S2, indicate an accurate predictive performance of the final model regarding both the structural and stochastic model for obese and non-obese subjects.

5.3.3 Dose evaluations

Simulation results of the recommended fluconazole IV dosage regimen for invasive candidiasis in Figure 3 indicate that heavier subjects have lower steady-state exposure compared with lighter subjects. Moreover, male subjects have lower exposure early after treatment initiation compared with female subjects of the same weight and it takes longer for male and heavier subjects to reach steady state in comparison with female and lighter subjects. Figure 4 presents the distribution of fluconazole $AUC_{24\ h}$ versus TBW on Day 1 and Day 7. With this regimen, all female subjects and 90% of male subjects lighter than 140 kg achieved the target of $AUC_{24\ h}$>200 mg·h/L on Day 1, and all individuals achieved this target at steady state. However, only subjects lighter than 80 kg obtained the target of $AUC_{24\ h}$>400 mg·h/L for the treatment of *Candida* meningitis or encephalitis at steady state.

To ensure that all subjects receiving fluconazole IV achieve the target of AUC_{24h}>200 mg·h/L on the first day of treatment, male subjects heavier than 140 kg need a higher loading dose of 600 mg twice daily, compared with 800 mg once daily (Figure 5). To achieve an $AUC_{24\ h}$>400 mg·h/L at steady state, the fixed IV maintenance dose has to be increased from 400 to 600 mg per day for all patients (Figure S3). To achieve this high target on the first day, doses above 1600 mg, which are deemed potentially unsafe, are needed for most patients, particularly for male subjects (Figure S3).

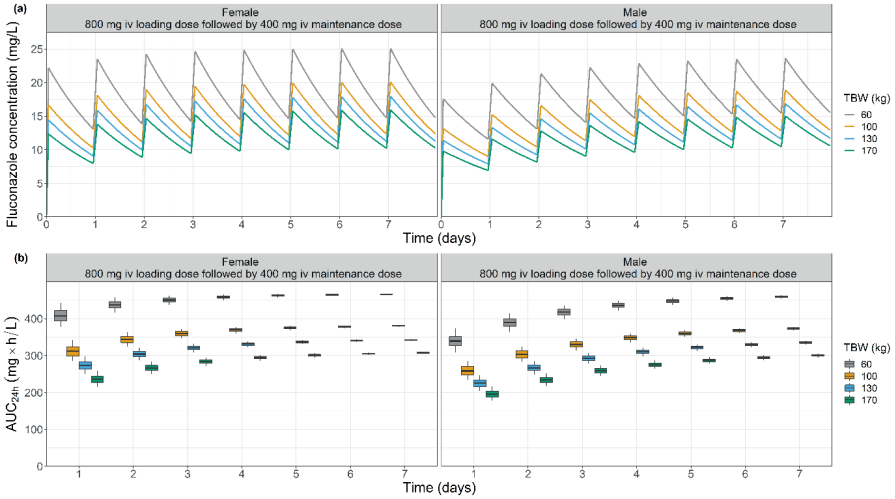

Figure 3. Median fluconazole concentration–time profiles (a) and distribution of the $AUC_{24\ h}$ (b) based on 1000 simulations of female and male subjects of various TBWs receiving a recommended IV loading dose of 800 mg once daily followed by a maintenance dose of 400 mg once daily. The boxes represent the 25th, 50th (median) and 75th percentiles, and whiskers represent the 5th and 95th percentiles (i.e. 90% distribution interval).

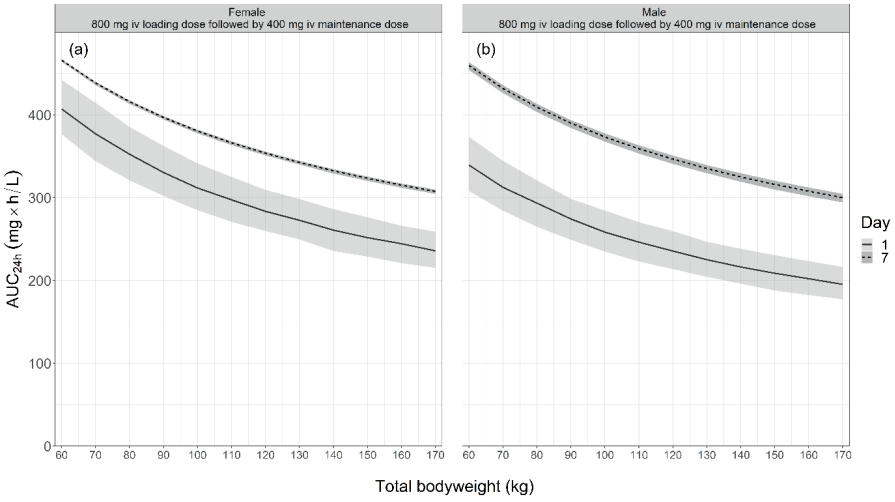

Figure 4. Distribution of $AUC_{24\ h}$ values versus TBW for fluconazole on Day 1 (solid line) and Day 7 (dashed line) based on 1000 simulations in female (a) and male (b) subjects receiving an IV loading dose of 800 mg once daily followed by a maintenance dose of 400 mg once daily. The shaded areas represent the 90% prediction interval.

Figures 5.6 and 5.7 present simulation results for a commonly used oral dosing regimen prescribed for treating oropharyngeal or oesophageal candidiasis. Due to the high IIV on F, exposure is highly variable for all weights. With the lower dose and variable F, no obese individual achieved the target of AUC24 h>200 mg·h/L. Other frequently used fluconazole oral dosing regimens were evaluated and the results can be found in Figures 5.S4–S7.

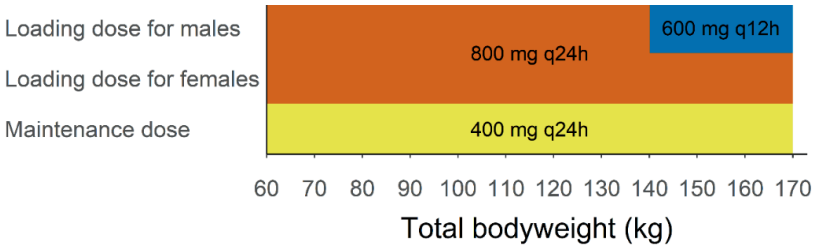

Figure 5. Model-derived IV loading and maintenance dose recommendations for fluconazole for achieving a target $AUC_{24\ h}$>200 mg·h/L for the first day of treatment in female and male subjects of various TBWs.

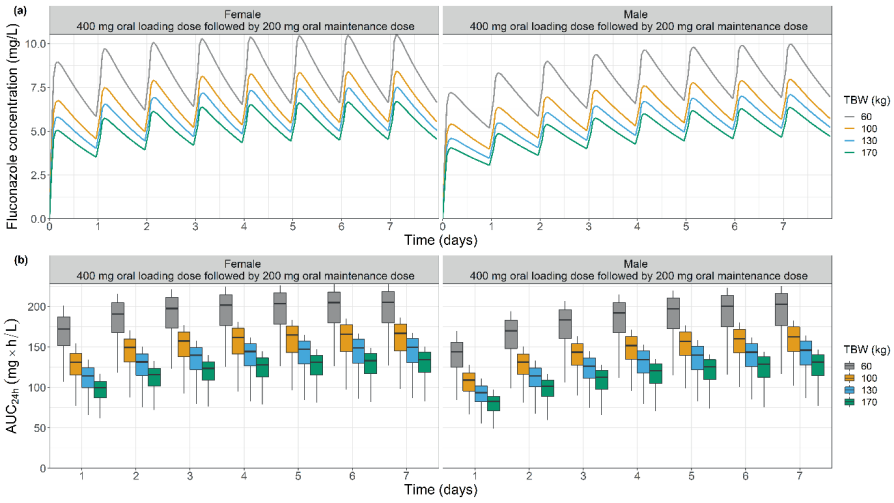

Figure 6. Median fluconazole concentration–time profiles (a) and distribution of the $AUC_{24\ h}$ (b) based on 1000 simulations of female and male subjects of various TBW receiving a recommended oral loading dose of 400 mg once daily followed by a maintenance dose of 200 mg once daily. The boxes represent the 25th, 50th (median) and 75th percentiles, and whiskers represent the 5th and 95th percentiles (i.e. 90% distribution interval).

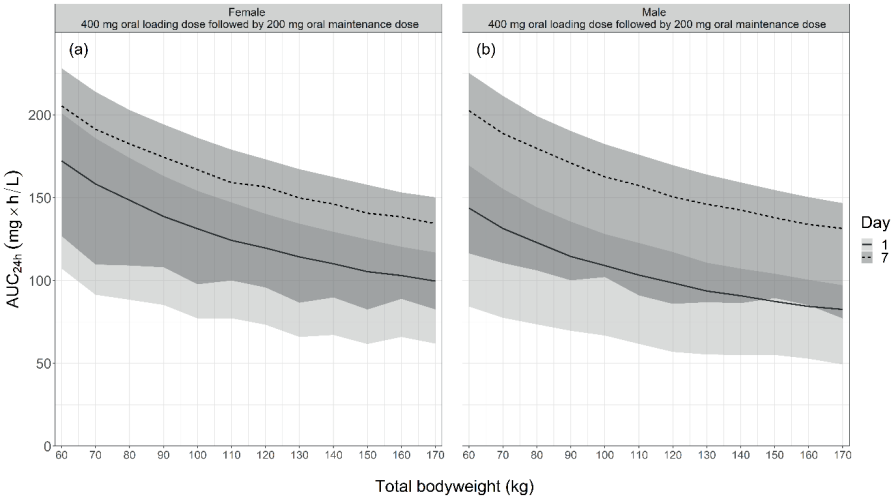

Figure 7. Distribution of $AUC_{24\,h}$ values versus TBW for fluconazole on Day 1 (solid line) and Day 7 (dashed line) based on 1000 simulations in female (a) and male (b) subjects receiving an oral loading dose of 400 mg once daily followed by a maintenance dose of 200 mg once daily. The shaded areas represent the 90% prediction interval.

5.4 Discussion

This study shows that obesity alters fluconazole pharmacokinetics. The typical F of fluconazole capsules (87.5%) is within the reported range of 78%–162%,[36] and no statistically significant difference was identified on the F or absorption rate constant between the obese and non-obese, indicating that obesity has a very limited influence on the rate and extent of absorption of fluconazole capsules. Despite a high average F for fluconazole capsules, caution should be taken when switching from IV to the oral capsule due to the high IIV in F. In obese adults up to 174 kg, TBW is significantly correlated with V_d and CL, which can be described with power functions (Table 2). Additionally, the V_d in male subjects is on average 26.9% larger than in female subjects of the same weight.

Only a few studies investigated fluconazole in the obese population. Alobaid *et al.*[37] investigated the pharmacokinetics of fluconazole in critically ill obese patients. Although no statistically significant covariate relationship was found from this study, the measured CL_{CR} was included as a covariate on CL merely due to the improvement in the diagnostic plots and, similarly, BMI was used as a descriptor for V_d of the central compartment based on biological plausibility and improvement from the diagnostic plots. The small sample size in this study and the pathophysiological complexity of critically ill patients might have obscured the impact of obesity. An important strength of our study is the prospective study design with semi-simultaneous oral and IV dosing, which allows for an accurate estimation of F by reducing the influence of inter-

occasion variability, the intensive sampling and the wide range of TBW. By selecting relatively healthy individuals, the potentially confounding influence of pathological factors such as renal dysfunction is circumvented; however, this comes with the limitation that extrapolations to patients, particularly patients with renal dysfunction or other relevant pathological factors, cannot be made directly. Although the bariatric surgery during this pharmacokinetic study might interfere with the pharmacokinetics, we anticipate that this influence may be negligible as the duration of this surgery is short (<1 h) with minor blood loss (<50 mL). Although the population CL in the healthy obese patients from our study is very similar to what has been reported in the critically ill obese patients (0.908 versus 0.950 L/h), a high IIV of 50.5% on CL was found in the patients while no IIV on CL could be identified by our model,[37] which suggests it may be more challenging to dose critically ill obese patients with whom multiple comorbidities are commonly associated. Pharmacokinetics studies conducted in various patient populations identified that kidney function and disease severity are associated with fluconazole CL.[37-40] We have not found kidney function estimates to be statistically significant predictors of IIV, which is likely attributable to the absence of individuals with impaired renal function. Additionally, in our model, the fluconazole CL of a 70 kg healthy individual is 0.908 L/h, corresponding to 15.1 mL/min, which is much lower than the average GFR in our population. This is in line with previous reports on extensive passive tubular reabsorption of fluconazole.[41] Although concentrations at 48 h were mostly missing from the obese group, no clear change in the elimination profile was noticed from 24 to 48 h based on the available concentrations at 48 h. Additionally, the estimation results of the final model remain similar when all concentrations at 48 h were excluded. Therefore, we do not expect that these missing observations at 48 h would alter our findings.

In addition to TBW, we found sex to be correlated with V_d. Interestingly, as sex is incorporated in the calculation of LBW, a similar descriptive potential of IIV in V_d could be obtained with LBW in comparison with the combination of TBW and sex. The contribution of height in the calculation of LBW appears to be negligible in our analysis, possibly because the range in height covers a difference of less than 30 cm. We decided to include the combination of TBW and sex to facilitate the clinical implementation of model-derived dosing recommendations by avoiding complex calculations of LBW. Higher body fat composition, namely a lower body water composition in female versus male subjects with the same TBW, could potentially explain the smaller V_d in female subjects.[42] Due to the increased V_d, obese male subjects with TBW ≥140 kg need an increased loading dose (Figure 5) to achieve target exposure on the first day of treatment.

With the dosing recommendations for obese patients as derived in our study (Figure 5), the target of $AUC_{24\,h}$/MIC>100 for a pathogen with MIC≤2 mg/L can be achieved. This recommendation is anticipated to be safe as a 1200 mg daily dose for 2 weeks has shown good tolerance and no liver function disturbance in 30 HIV patients.[43] A recent pharmacokinetic study in critically ill obese patients suggested a TBW-based

loading dose of 12 mg/kg and a maintenance dose of 6 mg/kg for pathogens with an MIC of 2 mg/L. With this dosing strategy, a loading dose >1600 mg is required in patients with TBW>130 kg, which is partly unnecessary according to our simulation (Figure 5) and potentially unsafe.[35] For the empirical treatment of *Candida* meningitis or encephalitis, a higher exposure might be desirable to compensate for the 20%–50% reduced fluconazole penetration into the CSF.[32, 33] Therefore we also assessed PTA for an $AUC_{24\ h}$ target of 400 mg·h/L, and the simulation results indicate that an increased maintenance dose of 600 versus 400 mg once daily is required, and loading doses exceeding 1600 mg for female subjects ≥140 kg and male subjects ≥90 kg to meet this target on Day 1 (Figure S3).[35] Clinicians should balance potential fluconazole-related toxicity with the decreased PTA when treating obese patients with *Candida* infections in the CNS.

We investigated the exposure levels for three commonly used fluconazole oral regimens including a loading (first day)/maintenance dose of 400/200 mg, 200/100 mg and 150 mg every third day for a total of three doses (Day 1, 4 and 7) in the first week, and 150 mg weekly (Figures 5.6–5.7 and Figures 5.S4–S7), which are primary treatments for superficial and mucosal *Candida* infections. Hardly any individual with TBW between 80 and 170 kg reached the $AUC_{24\ h}$>200 mg·h/L target with these doses, yet favourable clinical responses have been reported, suggesting that a lower target exposure may be effective.[44, 45] This could potentially be explained by the sufficient penetration of fluconazole.[46] Alternatively, the susceptibility of *Candida* spp. to fluconazole could be increased, or the immune response is more active with these infections. Symptomatic relapse of vulvovaginal candidiasis was reported in approximately 40% of women,[31] while the recurrent oropharyngeal and oesophageal candidiasis have also become an increasingly prevalent clinical issue.[44] Potentially these refractory superficial infections might result from the highly variable F we observed in obese and non-obese individuals, which means that a certain proportion of patients can be underexposed because they have a low F that could even exacerbate the infection by selecting more resistant strains of *Candida* spp.

5.5 Conclusion

Our results show that in otherwise healthy obese adults, both fluconazole CL and V_d increase with increasing TBW, with sex being an additional covariate for the V_d, resulting in a larger V_d in male compared with female subjects of the same weight. As a result, male subjects with high TBW may need increased loading doses as the time to steady state is longer. Model-based evaluations of commonly used oral dosing regimens illustrate high variability in exposure due to the high IIV in F, which could put large proportions of obese individuals at higher risk of underexposure.

5.6 Supplementary materials

Table S1. Equations used for calculating body size measures.

Body size measure	Equation	Referen
Body mass index (BMI), kg/m^2	$BMI = \frac{TBW(kg)}{Height(m)^2}$	
Body surface area (BSA), m^2	$BSA = TBW(kg)^{0.425} \times Height\ (cm)^{0.725} \times 0.007184$	[18]
Lean bodyweight (LBW), kg	$LBW_{male} = \frac{9270 \times TBW}{6680\ +\ 216\ \times\ \mathrm{BMI}}$	[26]
	$LBW_{female} = \frac{9270 \times TBW}{8780\ +\ 244\ \times\ \mathrm{BMI}}$	
Ideal bodyweight (IBW), kg	$IBW_{male} = 50 + 2.3 \times (Height(\mathrm{cm}) \times 0.3937 - 60)$	[28]
	$IBW_{female} = 45.5 + 2.3 \times (Height(\mathrm{cm}) \times 0.3937 - 60)$	
Adjusted bodyweight (ABW), kg	If TBW ≥ IBW, ABW = IBW + 0.4 × (TBW - IBW)	[28]
	If TBW < IBW, ABW = IBW	

Table S2. Equations used for calculating renal function indices.

Renal function index	Equation	Reference
Glomerular filtration rate (GFR), mL/min	$\text{GFR} = \frac{\text{Ucr}(\mu mol/L)}{\text{Scr}(\mu mol/L)} \times \frac{urine\ volume\ (mL)}{collection\ time\ (min)}$	[13]
Chronic Kidney Disease Epidemiology (CKD - EPI), mL/min/1.73 m^2	$\text{CKD-EPI}_{\text{male, nonblack}} = 141 \times \min\left(\frac{\text{Scr}(mg/dL)}{0.9}, 1\right)^{-0.411} \times \max\left(\frac{\text{Scr}(mg/dL)}{0.9}, 1\right)^{-1.209} \times 0.993^{AGE}$	[15]
	$\text{CKD-EPI}_{\text{female, nonblack}} = 141 \times \min\left(\frac{\text{Scr}(mg/dL)}{0.7}, 1\right)^{-0.329} \times \max\left(\frac{\text{Scr}(mg/dL)}{0.7}, 1\right)^{-1.209} \times 0.993^{AGE} \times 1.018$	
	$\text{CKD-EPI}_{\text{male, black}} = 141 \times \min\left(\frac{\text{Scr}(mg/dL)}{0.9}, 1\right)^{-0.411} \times \max\left(\frac{\text{Scr}(mg/dL)}{0.9}, 1\right)^{-1.209} \times 0.993^{AGE} \times 1.159$	
	$\text{CKD-EPI}_{\text{female, black}} = 141 \times \min\left(\frac{\text{Scr}(mg/dL)}{0.7}, 1\right)^{-0.329} \times \max\left(\frac{\text{Scr}(mg/dL)}{0.7}, 1\right)^{-1.209} \times 0.993^{AGE} \times 1.018 \times 1.159$	
De-indexed CKD-EPI, mL/min	$\text{CKD-EPI-di} = \frac{\text{CKD-EPI} \times \text{BSA}(m^2)}{1.73}$	
Modifcation of Diet in Renal Disease (MDRD), mL/min/1.73 m^2	$\text{MDRD}_{\text{male, nonblack}} = 175 \times \left(\text{Scr}(mg/dL)\right)^{-1.154} \times AGE(years)^{-0.203}$	[14]
	$\text{MDRD}_{\text{female, nonblack}} = 175 \times \left(\text{Scr}(mg/dL)\right)^{-1.154} \times AGE(years)^{-0.203} \times 0.742$	
	$\text{MDRD}_{\text{male, black}} = 175 \times \left(\text{Scr}(mg/dL)\right)^{-1.154} \times AGE(years)^{-0.203} \times 1.212$	
	$\text{MDRD}_{\text{female, black}} = 175 \times \left(\text{Scr}(mg/dL)\right)^{-1.154} \times AGE(years)^{-0.203} \times 0.742 \times 1.212$	
De-indexed MDRD, mL/min	$\text{MDRD-di} = \frac{\text{MDRD} \times \text{BSA}(m^2)}{1.73}$	
Cockcroft-Gault with TBW, mL/min	$\text{CG-TBW}_{\text{male}} = \frac{(140 - age(years)) \times TBW(kg)}{72 \times \text{Scr}(mg/dL)}$	[16]
	$\text{CG-TBW}_{\text{female}} = \frac{(140 - age(years)) \times TBW(kg)}{72 \times \text{Scr}(mg/dL)} \times 0.85$	
Cockcroft-Gault with LBW, mL/min	$\text{CG-LBW}_{\text{male}} = \frac{(140 - age(years)) \times LBW(kg)}{72 \times \text{Scr}(mg/dL)}$	[17]
	$\text{CG-LBW}_{\text{female}} = \frac{(140 - age(years)) \times LBW(kg)}{72 \times \text{Scr}(mg/dL)} \times 0.85$	

Ucr urine creatinine, *Scr* serum creatinine

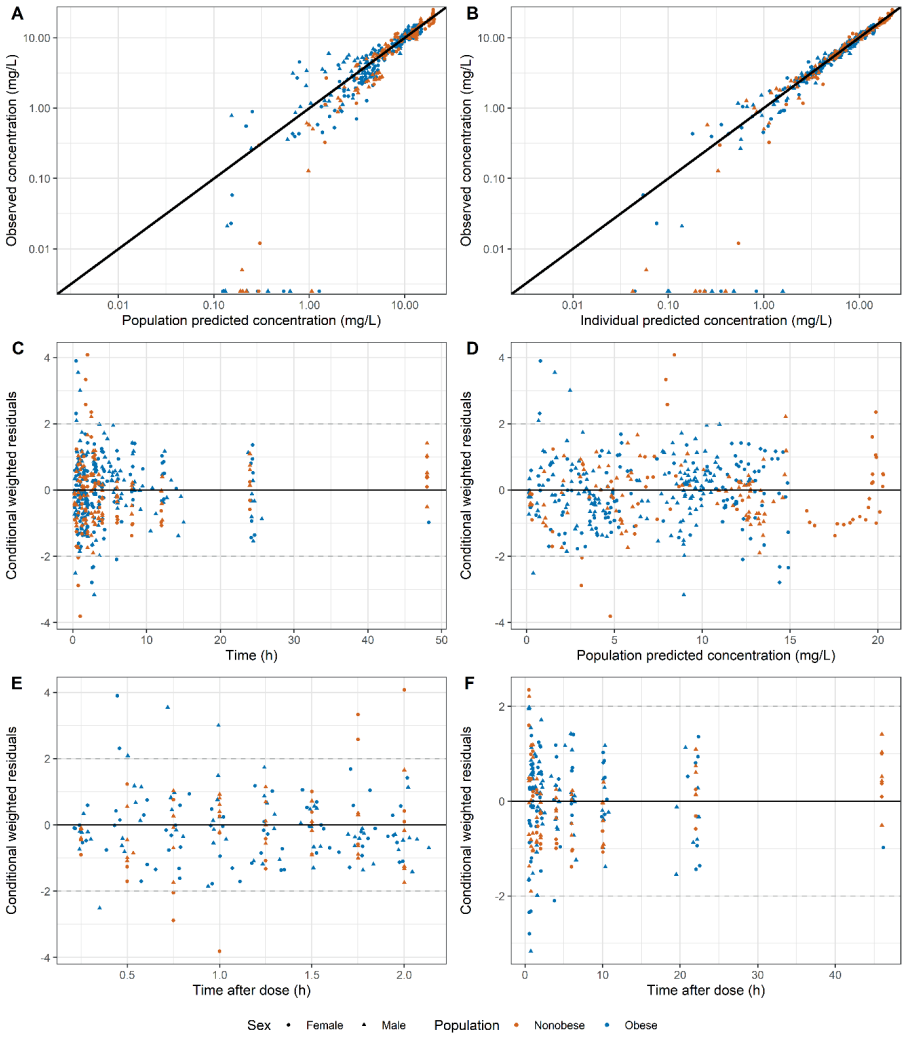

Figure S1. Goodness-of-fit plots of the final population pharmacokinetic model of fluconazole: observed *versus* individual predicted fluconazole concentrations (**A**), observed *versus* population predicted fluconazole concentrations (**B**), conditional weighted residuals *versus* time after first (oral) fluconazole administration (**C**), conditional weighted residuals *versus* population predicted fluconazole concentrations (**D**), conditional weighted residuals *versus* time after dose for observations after the oral dose only (**E**), conditional weighted residuals *versus* time after dose for observation after the iv infusion (**F**).

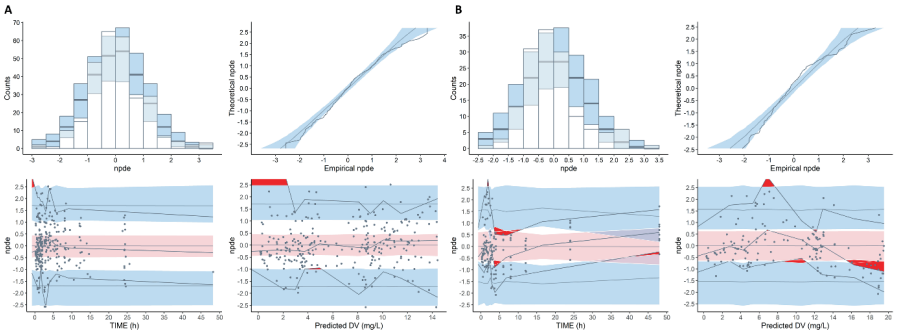

Figure S2. Normalized prediction distribution error (NPDE) results of the final model (n = 1000) stratified for obese (**A**) and non-obese (**B**) subjects. In plots of NPDE *versus* Time and NPDE *versus* Predicted DV, each prediction interval (95%) is plotted as a colored area (blue for the 2.5 and 97.5th percentiles and pink for the median). The corresponding 2.5th, 50th, and 97.5th percentiles of the observed data are plotted as jagged lines. The outliers of the bounds of the confidence interval are highlighted in red.

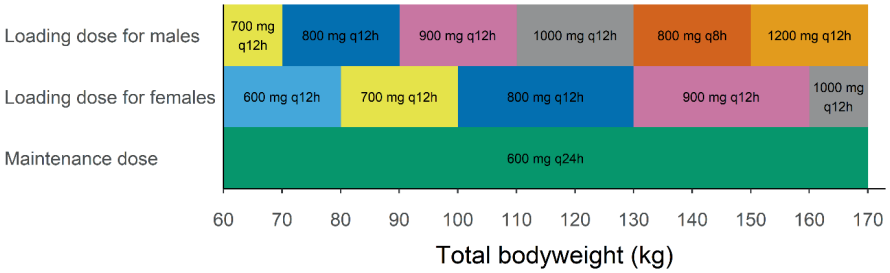

Figure S3. Simulation-based iv loading dose and maintenance dose of fluconazole for achieving the target of AUC_{24h} > 400 mg*h/L in female and male subjects of various total bodyweight. Target attainment for fluconazole loading dose and maintenance dose was assessed on day 1 and day 7, respectively. A total daily dose of up to 1600 mg was reported to be well tolerated in patients, above which neurological toxicity was observed.[35]

q24h dose every 24 h, *q12h* dose every 12h, *q8h* dose every 8h.

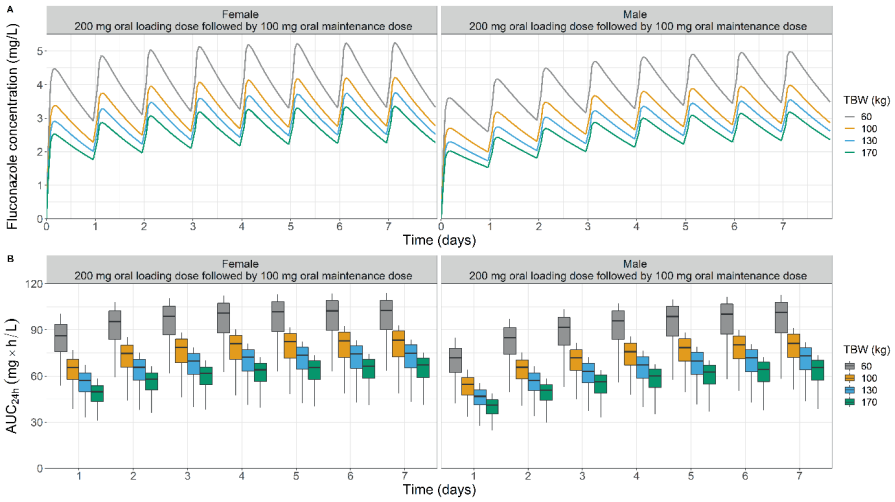

Figure S4. Median fluconazole concentration-time profiles (**A**) and distribution of the area under the curve per day (AUC_{24h}) (**B**) based on 1000 simulations of female and male subjects of various total bodyweight (TBW) receiving a recommended oral loading dose of 200 mg once daily followed by a maintenance dose of 100 mg once daily. The boxes represent the 25th, 50th (median), and 75th percentiles, and whiskers represent the 5th and 95th percentiles (i.e. 90% distribution interval). This dosage yields half of the exposure compared with the 400-200 mg regimen as presented in Figure 6.

Note: the scale on the y-axis is different from the scales of the figures in the main text.

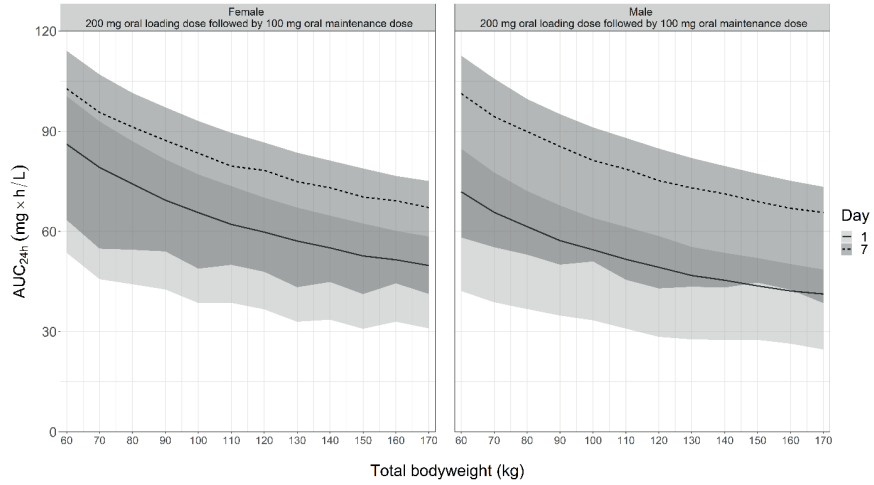

Figure S5. Distribution of AUC_{24h} values *versus* total bodyweight (TBW) for fluconazole on day 1 (solid line) and day 7 (dashed line) based on 1000 simulations in female (left) and male (right) subjects receiving an oral loading dose of 200 mg once daily followed by a maintenance dose of 100 mg once daily. The shaded areas represent the 90% prediction interval. This dosage yields half of the exposure compared with the 400-200 mg regimen as presented in Figure 7.

Note: the scale on the y-axis is different from the scales of the figures in the main text.

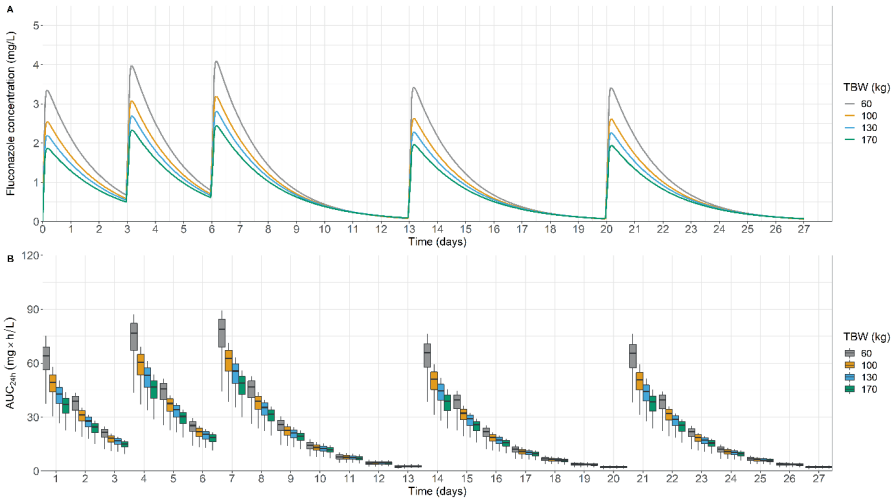

Figure S6. Median fluconazole concentration-time profiles (**A**) and distribution of the area under the curve per 24-h (AUC_{24h}) (**B**) based on 1000 simulations of female subjects of various total bodyweight (TBW) receiving an oral loading dose of 150 mg every third day for a total of 3 doses (day 1, 4, and 7) followed by a maintenance dose of 150 mg once weekly for treating recurrent vaginal candidiasis for 28 days. The boxes represent the 25th, 50th (median), and 75th percentiles, and whiskers represent the 5th and 95th percentiles (i.e. 90% distribution interval). The simulation results showed that the average maximum concentrations (C_{max}) for all individuals are below 5 mg/L and the corresponding AUC_{24h} is less than 100 mg*h/L.

Note: the scale on the y-axis is different from the scales of the figures in the main text

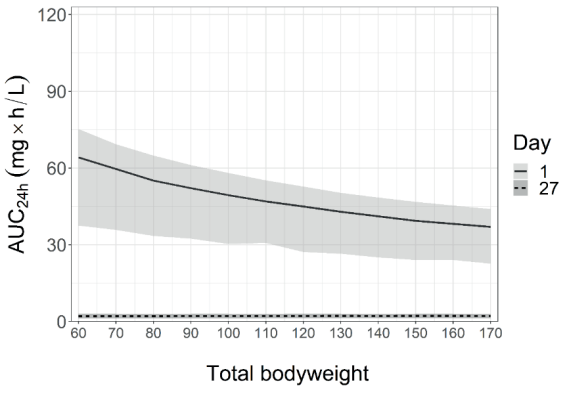

Figure S7. Distribution of AUC_{24h} values *versus* total bodyweight (TBW) for fluconazole on day 1 (solid line) and day 27 (dashed line) based on 1000 simulations in female subjects receiving an oral loading dose of 150 mg every third day for a total of 3 doses (day 1, 4, and 7) followed by a maintenance dose of 150 mg once weekly for treating recurrent vaginal candidiasis for 28 days. The shaded areas represent the 90% prediction interval.

Note: the scale on the y-axis is different from the scales of the figures in the main text.

NONMEM Control Stream for the Final Model

```
$PROBLEM Fluconazole PK in obese and non-obese
$INPUT ID TIME AMT RATE DV LNDV MDV EVID CMT TAD OBESE ORAL IVDURA RATE1 DOSETIME PKNO IDORAL IDPK SEX AGE
WT HT BMI BSA LBW IBW ABW OBESEHIS OBESEAGE HEMT0 CREAT0 TBIL0 ALP0 ALT0 AST0 GGT0 URCREAT CKD0 CKDdi0
MDRD0 MDRDdi0 CGTBW0 CGLBW0 GFR
$DATA LC_Fluconazole_17obese_8HV_oral_iv_PK_LLOQ0.0025.csv IGNORE=@
$SUB ADVAN13 TOL=9
$MODEL
COMP=(DEPOT)
COMP=(CENTRAL)
COMP=(TRANS1)
COMP=(TRANS2)

$PK
KTR = THETA(1)*EXP(ETA(1))
TVV2 = THETA(2)*(WT/70)**THETA(5)*(1+THETA(6)*SEX)
V2 = TVV2*EXP(ETA(2))
TVCL = THETA(3)*(WT/70)**THETA(7)
CL = TVCL*EXP(ETA(3))
TVF = THETA(4)
LGTBIO=LOG(TVF/(1-TVF))
LGBIO=LGTBIO+ETA(4)
F1= EXP(LGBIO)/(1+EXP(LGBIO))
K10 = CL/V2
S2 = V2

$DES
DADT(1)= -KTR*A(1)
DADT(2)= KTR*A(4) - K10*A(2)
DADT(3)= KTR*A(1) - KTR*A(3)
DADT(4)= KTR*A(3) - KTR*A(4)

$ERROR
IPRED = F
Y = IPRED * (1 + EPS(1)) + EPS(2)

$THETA
(0, 2.69) ; 1 KA
(0, 38.5) ; 2 V2
(0, 0.908) ; 3 CL
(0, 0.875,1) ; 4 F1
(0, 0.567) ; 5 WT/70 power on V2
(-1, 0.269) ; 6 SEX on V2
(0, 0.39) ; 7 WT/70 power on CL

$OMEGA
0.192 ; 1 KA
0.00526 ; 2 V2
0 FIX ; 3 CL
1.25 ; 4 F1

$SIGMA
0.0033 ; Proportional
0.266 ; Additive 0.1 ; Additive

$EST PRINT=5 MAX=9999 METHOD=1 NSIG=3 SIGL=6 INTERACTION POSTHOC NOABORT MSFO=mfi
$COV PRINT=E
$TABLE ID TIME AMT RATE DV LNDV MDV EVID CMT TAD OBESE ORAL IVDURA RATE1 DOSETIME PKNO IDORAL IDPK SEX AGE WT
HT BMI BSA LBW IBW ABW OBESEHIS OBESEAGE HEMT0 CREAT0 TBIL0 ALP0 ALT0 AST0 GGT0 URCREAT CKD0 CKDdi0 MDRD0
MDRDdi0 CGTBW0 CGLBW0 GFR LLOQ KTR V2 CL F1 ETAS(1:LAST) IPRED PRED CWRES NOAPPEND NOPRINT ONEHEADER
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Chapter 6

Summary, lessons learned, perspectives, and overall conclusions

6.1 Summary

Invasive fungal diseases (IFDs) are hidden killers, particularly for immunocompromised patients. Despite recent advances in the diagnosis and treatment of IFDs, the mortality from these diseases remains high. Developing a new antifungal drug is often lengthy and costly, suggesting that maximizing the efficacy of currently available medications is key.

In Chapter 1, we provided an overview of the current treatment options for the IFDs [1]. An exposure-response relationship has been demonstrated for all triazoles. Even so, clinicians still encounter various issues regarding safety and/or (lack of) efficacy in practice, which – among others - result from the highly variable drug exposure levels. To better address them, it is essential to understand the pharmacokinetics (PK) of these triazole agents. This thesis investigated the population PK profiles of two commonly used triazole antifungals, i.e., posaconazole and fluconazole, with a special focus on oral absorption and oral bioavailability (F), to provide scientific evidence on optimal dosing.

Chapter 2 summarized the existing knowledge on posaconazole PK, pharmacodynamics (PD), toxicity, resistance, clinical experience in special populations, and new therapeutic strategies. Posaconazole shows high variability in exposure within patients, but also between the three available formulations, between healthy volunteers and patients, and between different patient populations. Despite administration of a lower daily dose, the two newest formulations, i.e., delayed-released tablet (DR-tablet) and intravenous (IV) formulation, yield higher and more stable exposure than the oral suspension. For this reason, the DR-tablet is often preferred over suspension in practice. However, an integrated analysis comparing posaconazole PK differences among various formulations and populations is still lacking.

To bridge the knowledge gaps identified in Chapter 2, we first characterized the population PK, including the absolute F, of all posaconazole formulations with a focus on healthy volunteers, to circumvent the potentially confounding influence of pathological and clinical factors, in **Chapter 3**. For the oral suspension, the impact of food on both F and absorption rate, as well as a dose-nonlinearity in F, were quantified, resulting in lower F under fasted conditions or when given in a higher dose. Food intake also significantly boosts the F of DR-tablet. The tested concomitant medications, including antacid, ranitidine, esomeprazole, and metoclopramide, had no statistically significant impact on the absorption of the DR-tablet. With a higher and more stable F, the PK superiority of the posaconazole DR-tablet, compared with the oral suspension, was demonstrated. Administering the DR-tablet under fasted conditions however results in a lower-than-expected F, suggesting that administering the DR-tablet with food should be considered, to enhance absorption and ensure sufficient exposure. Model-based simulations in healthy volunteers illustrate that when administered under fasted conditions, more than 35% of individuals receiving

the licensed prophylactic dose of the oral suspension or DR-tablet are at risk of suboptimal exposure.

As considerable differences between healthy volunteers and patients are known, we expanded the integrated PK analysis from the healthy population to (mainly) hematological patients in **Chapter 4**. In patients, the F of the DR-tablet is overall higher than the dose-dependent nonlinear F of the oral suspension and is unaffected by the tested covariates. Five clinical characteristics were found to significantly reduce the F of the oral suspension, including mucositis, diarrhea, administration through a nasogastric tube, and concomitant use of proton pump inhibitors or metoclopramide. Additionally, patients showed a larger peripheral volume of distribution and lower inter-compartmental clearance compared to healthy volunteers, resulting in decreased trough concentrations for all formulations. Patients with hypoalbuminemia showed lower clearance (CL). No racial differences in PK could be found between Chinese and Caucasian patients, suggesting that Chinese patients do not require a different dose compared to Caucasian patients. Though superior to the oral suspension, the F of the DR-tablet is lower than previously reported, meaning that exposure upon administration of the same dose is not equivalent to IV. Switching to IV or increasing the dose of the DR-tablet coupled with therapeutic drug monitoring, should therefore be considered to ensure optimal exposure.

Posaconazole is most widely used for mould-active prophylaxis. Yet fluconazole remains the most widely used antifungal agent in patients suspected or diagnosed with yeast infections such as candidiasis. It is used in a wide variety of individuals, including in patients with obesity. As a special population, subjects who are obese are often left out of pre- or post-marketing clinical trials. To close the knowledge gap of fluconazole prescription in the obese, in **Chapter 5**, we performed a prospective PK study in obese subjects and non-obese healthy controls who received a semi-simultaneous fluconazole oral capsule and IV dose. Based on the population PK, obesity had no impact on the F of the fluconazole oral capsule. Nevertheless, participants with higher total bodyweight were found to have both higher CL and volume of distribution. In addition to total bodyweight, we found sex also statistically significantly impacted the volume of distribution, resulting in a larger volume of distribution in males compared with female subjects of the same weight. As a result, male subjects with high total bodyweight may need increased loading doses to compensate for the slower accumulation of the drug in reaching steady state. The commonly used fluconazole oral dosing regimens illustrate high variability in exposure, likely putting large proportions of obese individuals at higher risk of underexposure. To facilitate the clinical implementation of our findings, we proposed dosing tables for female and male subjects of various total bodyweight.

6.2 Lessons learned

In this section, we summarize and discuss the lessons learned during the development and refinement of the population PK models from Chapters 3-5. Our objective is to contribute to the advancement of modeling practices by sharing our experiences and insights, thereby improving the efficiency and effectiveness of future modeling efforts.

6.2.1 Integrated population PK analysis

Integrated population PK analyses combining data on different formulations and populations should be advocated when feasible. Analyzing all data together, will maximize the benefit of shared information in the data and thereby allow identification of PK differences attributable to the formulations or/and populations. Such integrated population PK analysis can provide several benefits during drug development and for post-marketing studies. First, it can improve our understanding of drug behavior by providing a comprehensive understanding of how a drug behaves in different conditions, such as different dosing regimens or patients with different characteristics and it can avoid wrong conclusions being drawn based on partial data. Second, it can increase the efficiency of drug development, as an integrated analysis of healthy volunteer data in the early stages can help identify areas where further research is needed and allow for more efficient development of formulations or dosing regimens. This can save time and resources by avoiding unnecessary research efforts. Third, it may have a greater regulatory acceptance, as regulatory agencies often require integrated analyses when evaluating new drugs or applications [2]. Going beyond PK, it is expected that integrated analyses can also enhance safety and efficacy evaluations, by pooling data from multiple studies and thereby providing a more robust evaluation of safety and efficacy, particularly for rare adverse events or subpopulations that may not be adequately represented in individual studies. Unfortunately, such integrated analysis is not always implemented during drug development, while performing such analysis after marketing requires the industry to share its data which is typically a time-consuming effort. Facilitating post-marketing open data sharing might be a potential solution.

6.2.2 Using prior knowledge to inform population PK models

When quantifying PK features with limited data, one can either constrain the model based on existing data or broaden its applicability by incorporating prior knowledge from the literature. Literature data could also be used for the model evaluation. For example, in Chapter 3, dosing scenarios for the oral posaconazole suspension were limited to 100 mg under fed and fasted conditions and 400 mg under fed conditions only. During model development for the oral suspension, the available data could therefore only support a linear F with a binary food effect. However, the model obtained with this purely data-driven approach, overpredicted exposure for a dose

of 400 mg under fasted conditions by more than 100% compared with the exposure levels reported in the literature. Moreover, the impact of food was reported to increase with the increasing dose in the healthy volunteers, which cannot be captured by a binary food effect. To expand the applicability of our model to commonly used dosing scenarios, we used a decreasing sigmoidal function to characterize a continuous dose-nonlinear function for F with different parameter values for the sigmoidal function under fasted and fed conditions, to describe the dose-nonlinear impact of food. To deal with the limited available data in the dataset, literature information was included to inform the complex nonlinear functions for F, allowing parameter estimation. In addition to the regular internal model evaluation, we subsequently also compared the simulated area under the concentration-time curve (AUC) values and the ratio of AUC values to the reported literature values under different scenarios of doses and food intake. Using this approach, we were confident that the nonlinear functions for F, informed by both the available data and the meta-data from literature, could be used for both interpolation and extrapolation to clinically relevant dosing scenarios, which also facilitated the extension to the patient's PK in **Chapter 4**.

6.2.3 Simulation and re-estimation to assess parameter identifiability

Simulation and re-estimation approaches can help to assess parameter identifiability when there is a suspicion of limited information regarding certain model parameters in the data as a result of the associated study design. Model identifiability is categorized into two types; structural identifiability related to the structure of the model and deterministic identifiability related to the study design [3]. In **Chapter 5**, the absorption profiles after administration of the oral tablet in the semi-simultaneous oral and IV study showed absorption to not be fully completed when the IV dose was administered (Figure 1), leading to the suspicion that the sampling duration of the absorption phase might have been too short to support an accurate estimation of F. This would comprise deterministic identifiability issues. While there are limited software tools that are specifically created to evaluate structural identifiability, there is currently no dedicated software available for assessing deterministic identifiability [3]. In Chapter 5, we therefore performed a simulation and re-estimation analysis to assess the deterministic identifiability. To implement the simulation and re-estimation approach, we simulated the design of the original study under scenarios of two different values for F, one scenario in which F was 50% and another in which F was 90%, in both cases, interindividual variability was 1.69 (variance) in the logit domain. Subsequently, the model was re-estimated based on the simulated datasets. The re-estimated F obtained with these datasets was 57% and 92.5%, indicating a percentage bias of 14% and 3%, respectively. This confirmed that in this case, the applied study design was sufficient to obtain an accurate estimate of F despite the limited observation period after oral dosing before the intravenous dose was given. Even though this approach allowed us to confirm the identifiability of fixed effect parameters in our analysis, parameter identifiability should be ideally considered in the design phase of a study. In addition to the existing software that has been

developed for an optimal design of experiments [4, 5], this proposed simulation and re-estimation approach can also be considered in helping select a design that fulfills the requirements for deterministic identifiability. It has to be noted that an appropriate model structure and appropriate parameter values are prerequisites for any approach, otherwise, the results can be misleading. A recently released design evaluator in NONMEM ($DESIGN) provides parameter estimability or expected model parameter uncertainty by assessing the Fisher Information Matrix [6], which can be a more efficient approach compared with the simulation re-estimation approach to investigate deterministic variability.

6.2.4 Close inspection of diagnostic plots

During model development, close inspection of diagnostic plots, including appropriate subsets of the data, is an indispensable addition to numerical diagnostics in model selection. In **Chapter 5**, we investigated the model fit when using the different numbers of transit compartments in describing the absorption profile of the fluconazole capsule. As shown in Figure 1 below, the lowest objective function value (OFV) was obtained with the model with six or seven absorption transit compartments. As expected, the parameter estimate of the first-order rate constant between absorption transit compartments (k_{tr}) increased with the increasing number of transit compartments, Yet during the absorption phase, these two models also showed time-related trends in the diagnostic plot of conditional weighted residuals *versus* the time after dose, which was not present in the model with three transit compartments. Based on these plots, the model with three transit compartments was selected, even though it had not reached the lowest statistically significant objective function value (see Figure 1). Of note is that the bias in the 2.5-hour absorption phase is easily overlooked when only examining the plots of the entire 48-hour time span of the study. This illustrates the importance of a detailed investigation of subsets of the data, as the absorption model selected based on a detailed investigation of the data in the absorption phase not only yielded an optimal description of the data in the absorption phase but also yielded more realistic estimates of the remaining PK parameters. For other drugs for which rich data is available in the absorption phase, it may be equally important to investigate and optimize the absorption model to achieve an unbiased fit, in which a lower OFV value does not always mean a more precise model fit and close inspection in diagnostic plots, like Figure 1, should be performed.

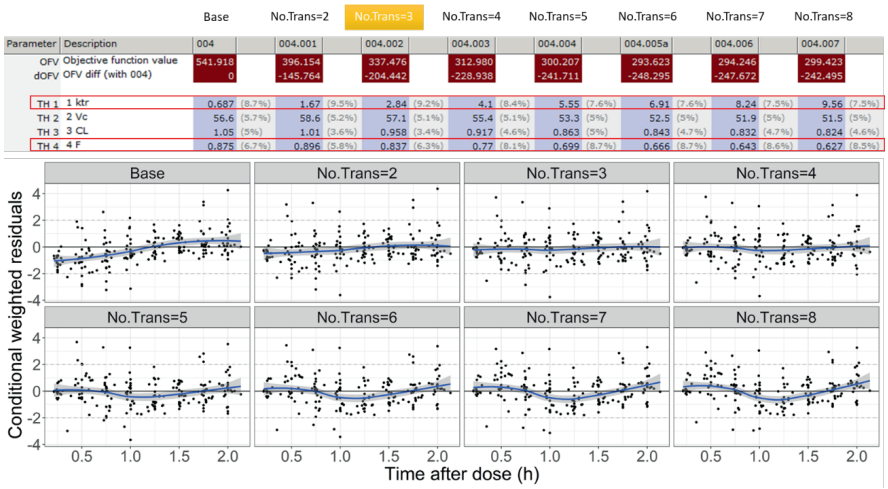

Figure 1 Overview of obtained fluconazole PK fixed effect parameter estimates (top) and the corresponding conditional weighted residuals *versus* the time after dose plots (bottom) in a first-order absorption model without transit compartment (Base) compared with those in models incorporating absorption delay using two to eight transit absorption compartments.

No.Trans = number of transit compartments, *OFV* = objective function value, *ktr* = first-order rate constant between absorption transit compartments (h^{-1}), *Vc* = volume of distribution in the central compartment (L), *CL* = clearance (L/h), *F* = bioavailability (-).

Stratifying diagnostic plots across different subgroups or strata of a population is also important to inspect for possible bias both during model development as well for final model validation. This is to ascertain an accurate description of the data obtained across the entire population. Incorporating stratification into the eta and goodness-of-fit (GOF) plots is crucial. Splitting the eta and GOF for separate strata or using different colors for data points of individuals or observations with specific characteristics, can expose bias in subgroups at an early stage during model development and indicate the direction for model improvement. If we find that the model fits well across all subgroups, then we can confirm a good description of the model for the population as a whole. If, on the other hand, we find that the model fits well in some subgroups, but not in others, we may need to modify the model or investigate further to understand why this is the case. Visual predictive check (VPC) and normalized prediction distribution errors (NPDE) plots are often used to provide a more comprehensive assessment of the final model's ability to predict the data and may not only reveal issues in the structural model but also in the stochastic model. In this context, these plots can also be stratified for subpopulations.

It is even more important in an integrated analysis to stratify the diagnostic plots, because the bias can be easily overlooked when data from various subgroups are assembled in the same diagnostic plot. In **Chapter 3**, we stratified our GOF and NPDE results into 3 separate figures based on formulation, and in **Chapter 4**,

we stratified them based both on formulation and population (healthy population *vs*. patients). In **Chapter 5**, we found that both total bodyweight and sex have a significant influence on fluconazole PK, therefore we wanted to look at the residuals separately for men and women, and obese and non-obese groups (Figure S1). By doing this, we confirmed that the model fits equally well across different subgroups.

6.2.5 The added value of shark-plot in a covariate analysis

In a covariate analysis, the goal is to identify patient or treatment-specific variables, such as demographics, disease-related variables, or concomitant treatments, that are correlated with the variability in PK parameters. These covariates are typically included in the PK model as fixed effects. However, not all patients contribute to the covariate relationship in the same way. In exceptional cases, one or two patients may have extreme covariate values or have a low-frequency covariate, while their individual PK parameters deviate from the rest of the patients. As a result, it may seem that the tested covariate is statistically significant, while in reality it can be ascribed to a multi-factor influence or other (unknown) reasons. In the covariate analysis, the OFV provides statistical evidence based on the whole population but does not take the sensitivity of the individual contributions to the OFV difference into account. Shark-plot can be used to illustrate the contribution of each individual to the overall OFV differences between the model with the new covariate included and the reference model without the covariate and establish how many individuals drive the statistical significance of the difference [7].

Identifying influential individuals that drive covariate selection, with shark-plot can be useful in two ways. It can pinpoint the influential individuals who largely contributed to the statistical significance during the covariate analysis, opening the opportunity for further investigation. When a shark-plot shows only one or very few individuals are driving the statistical significance, in many cases, one should not include such a covariate relationship. It can either be that the causal relationship is missing (otherwise the other individuals would follow the same trend), or the study design/included individuals are not sufficient to differentiate between true correlation and spurious patterns, whereby the data are not sufficient to support conclusions Ignoring the influential individual during covariate analysis may lead to a final model with a weakly supported covariate relationship, which may yield unnecessary recommendations for dose adjustments. For this reason, we urge modelers to consider using a shark-plot during the covariate analysis.

6.3 Perspectives

In this thesis, we fill a few PK knowledge gaps of posaconazole and fluconazole using a population modeling approach. While our work covers solely PK, during the analysis and literature study, we identified a few crucial components that are not adequately addressed in current antifungal PK/PD analyses, such as free target site

drug concentration, antifungal drug resistance, and host immunity. Furthermore, we recognize the potential utility of another PK modeling approach, i.e., physiologically-based PK (PBPK) modeling, in characterizing oral drug absorption and PK in obese individuals. Our objective in this section is to draw attention to these underexplored areas in antifungal PK/PD analysis and emphasize the unique value of PBPK modeling in exploring drug absorption and PK in special populations. Eventually, we can have a more comprehensive understanding of the pharmacology of antifungal therapy and improve treatment outcomes across diverse patient populations.

6.3.1 Free target site drug concentration

The free drug concentration at the site of action is the main determinant of drug activity and is therefore considered to be a more relevant measure of drug exposure than the total plasma concentration. In many cases, total drug concentration in blood or plasma is a good proxy for the free fraction at the target site, for instance when there is no saturation of plasma protein binding or specific tissue binding or accumulation at the target site. Therefore, they are commonly used to establish the total PK profile of a drug in plasma.

In the context of antifungal treatment, sufficient free drug concentration at the site of infection is a key determinant of antifungal efficacy. This is because only the free drug can penetrate the fungal cell wall and reach the target site to exert its fungicidal or fungistatic activity. Some antifungal agents (e.g. itraconazole, posaconazole, micafungin) exhibit significant drug accumulation in pulmonary epithelial lining fluid and alveolar cells which are common infection sites for invasive aspergillosis, causing plasma levels to be unpredictive for target-site exposure [8, 9]. For posaconazole, free posaconazole also accumulates and persists within the membranes and the endoplasmic reticulum of the A. fumigatus cells where the azole target enzyme CYP51a is located [10]. In this case, significant drug accumulation with high variability was observed in the target tissue, meaning drug concentrations in the plasma cannot reliably serve as a surrogate of the exposure at the target site. Compared with the free plasma drug concentrations, which have received increasing recognition in clinical practice [11, 12], measuring free target site drug concentration can be more challenging. Fortunately, recent advances in technology, such as microdialysis facilitating sample collection in the respiratory tract or subcutaneous tissues, as well as ultrafiltration, ultracentrifugation, and equilibrium dialysis, facilitating quantifying unbound concentrations, together enabled more accurate and sensitive measurements of free drug concentrations. Incorporating these measured free target site drug concentrations in future PK/PD and PBPK studies can be a viable and effective resolution to better predict antifungal efficacy and understand the antifungal mechanism.

6.3.2 Antifungal drug resistance

Antifungal drug resistance is a growing concern, while the antifungal treatment options are rather limited [13]. PK/PD indices based on minimum inhibitory concentration (MIC), such as AUC/MIC, peak concentration *versus* MIC (C_{max}/MIC), and duration of time during which the concentration exceeds MIC (T>MIC), link the fungal sensitivity to antifungal exposure and are widely used to predict the clinical effectiveness and required dose of the antifungals in treating IFDs. The MIC measurement obtained by the conventional broth dilution method, while still widely used, relies on a limited number of tested concentrations of antifungal agents, which can limit its accuracy. With this approach, a static threshold of one single value is provided to represent the sensitivity of the pathogen colony against antifungals, which does not account for the diversity of the fungal population nor for changes over time resulting from the dynamics of fungal growth. Additionally, using a static summary of exposure such as the AUC, $C_{max,}$ or T>MIC in the PK/PD indices, precludes the investigation of how the dynamic changes in antifungal exposure affect susceptibility and resistance development.

The recent progress of more advanced and dynamic assays, such as impedance-based assays, in determining antibiotic susceptibility, provides more accurate results within hours and therefore allows real-time monitoring, which cannot be achieved by the static broth dilution method [14]. The impedance-based assays utilize the change in impedance caused by bacterial growth or death as an indicator of antibiotic susceptibility and provide faster detection with higher sensitivity of microbial activity and the bacterial response to antibiotics, which allows monitoring bacterial growth in real-time [14]. Although primarily tested in bacterial infections, this approach has exhibited promising potential for application in fungal infections [15]. By incorporating dynamic antibiotic susceptibility data, as well as the dynamic systemic and target site drug exposure and response profile, into a mechanistic PK/PD model, the dynamic drug-pathogen interaction can be captured. This model enables valuable insights into effective antifungal treatment against resistance.

6.3.3 Host immunity in antifungal treatment

In Chapter 2, we pointed out that host immunity plays an indispensable role in controlling and eradicating fungal infections. Most of the pathogenic fungi are opportunistic and as a result, they mainly cause IFDs in individuals under immunocompromised conditions. Many antifungal exposure-response relationships are developed based on data from *in vivo* neutropenic animals aiming to mimic human immunosuppression [16]. In practice, while neutropenia is a common feature of many immunocompromising conditions, such as chemotherapy-induced immunosuppression or prior to stem cell transplantation, it is not a universal feature. Moreover, the level of immune response in a patient can vary widely. For example, some patients may have only a mild decrease in their neutrophil count with remaining

function, while others may have severe neutropenia with functional loss of immune response. Consequently, the findings based on the neutropenic murine models only cover one subgroup of immune suppression seen in actual patients, thereby they have their limits when extrapolating to humans. To address this issue, incorporating host immunity into *in vivo* antifungal PK/PD analysis is the key.

Some researchers have proposed using mechanism-based models to integrate the time courses of the host immune response (such as IL6, IL8, and TNF-alfa profiles) with the infection biomarkers and real-time antimicrobial PK exposure. Such an integrated approach not only captures the interaction between the antimicrobials and the invading pathogen, i.e., the conventional PK/PD model but also incorporates the interaction between the pathogen and host immune system [17, 18], allowing the quantification of the dynamic change in the infection biomarkers and the variability from host immune response and antimicrobial PK. This concept has already been applied in the field of antibacterial treatment, with one approach being to include measures of host immune status, such as the patient's neutrophils, white blood cell count, or immune biomarkers including cytokines and chemokines, in the model [19-21]. In a manner akin to bacterial resistance, the immune system can also interfere with the emergence and progression of antifungal drug resistance. This is because the immune system does not distinguish between a resistant fungus and a susceptible one, thereby eliminating the residual pathogenic fungus aside from the elimination via antifungal agents, irrespective of their susceptibility level, which should be considered in future antifungal drug resistance studies as well.

Overall, incorporating host immunity into antifungal PK/PD models has the potential to improve our understanding of how antifungal drugs exert their antifungal efficacy in patients exhibiting diverse immune system conditions. Consequently, this advancement may facilitate the optimization of treatment strategies for fungal infections.

6.3.4 PBPK modeling in characterizing oral absorption and PK in obese population

PBPK modeling takes into account both the physicochemical properties of the drug and the physiological characteristics of different tissues and organs in the body, to predict drug disposition [22]. It can account for intestinal and hepatic enzyme activity, transporters, and other permeability-limited processes, which can be highly valuable in predicting the rate and extent of drug absorption, as well as the impact of food and other factors on these processes [23, 24]. Additionally, this modeling approach can also account for the free antifungal drug accumulation at the target site, which is a viable solution for the challenge discussed in section 6.3.1. Early PBPK modeling can help researchers make more informed decisions by identifying potential issues with the drug's absorption and making necessary chemical modifications (e.g. prodrug design), or modifications in formulation or dosing regimen. As a result, it can

facilitate the drug development process and help get effective treatments to patients more quickly. While PBPK modeling of drug absorption processes provides multiple advantages, it is highly complex and requires the collection of data regarding drug characteristics and physiological data. Although the physiological data are system-specific and therefore transferable to different scenarios, missing, incomplete, or unreliable drug-specific parameters, e.g., total unbound intrinsic CL by one microgram of metabolic microsomes, significantly impede the development of PBPK models. To address this challenge, it is imperative to consider mandating the acquisition of these drug-specific measurements as a standard practice within drug development or routine experimental protocols, ensuring the availability of pertinent and reliable drug-specific properties. Furthermore, the PBPK modeling methodology should be continually refined in alignment with the evolving knowledge in the field.

The influence of obesity on drug PK exhibits substantial variability across drugs with different drug properties, rendering it impractical to make predictions for this population using a single overarching principle [25-27]. While the global incidence of obesity keeps increasing, the obese population is often underrepresented in clinical trials compared to other special populations such as patients with renal or hepatic impairment. In this particular case, PBPK modeling which quantifies the physiological changes in body composition, blood flow, and organ function, in obese individuals compared to non-obese individuals, can be employed to conduct *in silico* clinical trials for drugs lacking clinical data in obese individuals. Pioneer researchers have taken the lead in developing the PBPK modeling framework for the obese population based on existing knowledge and investigating the parameter sensitivity of the drug dispositions in a few representative drugs [28]. Promising validation results on drug exposure have been obtained in several drug classes [29]. As promising as this approach may sound, certain critical parameters identified by the sensitivity analysis are still not accurately quantified in this special population, such as adipose tissue distribution, the abundance, and potency of metabolic enzymes and transporters in different tissues and organs, gastric emptying, and intestinal motility. This increases uncertainty in model prediction and therefore still limits its current application in this population. Future studies filling these knowledge gaps are essential to expanding the application of drugs associated with more complicated PK features.

6.4 Conclusions

This thesis investigated the PK of two triazole antifungal drugs, i.e., posaconazole and fluconazole, using a population modeling approach. The study began with a comprehensive review of existing knowledge on posaconazole PK, PD, major toxicity, resistance patterns, clinical experiences in special populations, and new therapeutic strategies. Identifying gaps in this knowledge, we proceeded to compare the PK profiles of all available pharmaceutical formulations of posaconazole in healthy volunteers through an integrated analysis. The analysis demonstrated DR-tablet's superiority compared with the oral suspension under both fed and

fasted conditions. To minimize the potential risk of inadequate drug exposure, we recommend administering both posaconazole oral suspension and DR-tablet with food. When extending the analysis to patients, we found that even though the DR-tablet exhibited higher and more stable F than the suspension, it did not achieve exposure levels equivalent to the intravenous form. A substantial risk of inadequate exposure was identified in a considerable proportion of hematological patients receiving oral posaconazole at the standard dose, irrespective of prophylaxis or treatment. To mitigate this risk, the option of switching to the IV formulation or increasing the DR-tablet dose, alongside therapeutic drug monitoring, should be considered to ensure sufficient drug exposure in these patients. Furthermore, our analysis revealed that obesity alters fluconazole PK. Consequently, we proposed a dosing table for clinicians to treat *Candida* infections in obese adults, which adds to the growing body of evidence on optimal dosing strategies for this underrepresented special population. Based on the modeling and simulation results of posaconazole and fluconazole, we identified high-risk scenarios for ineffective antifungal treatment and provided alternative treatment options and dosing advice. This may contribute to improving patient outcomes, aligning with the overarching goal of all pharmacometric modeling exercises.

Throughout the analysis, we learned new lessons and shared our insights to serve as a reference for other modelers in their decision-making processes during PK analysis. Free target site drug concentration, antifungal drug resistance, and host immunity are all essential yet unexplored, elements in antifungal treatment. Incorporating them into PK/PD modeling frameworks may provide insight into effective antifungal treatment. Additionally, PBPK modeling may provide valuable insights into drug absorption and disposition in the obese population by accounting for physiological changes, which can be a powerful tool to facilitate early-stage drug development and support decision-making regarding the selection of drug formulation or dosage regimens for further clinical studies.

6.5 References

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Samenvatting

Invasieve schimmelinfecties (ISI's) vormen een onderkend gevaar, met name voor immuungecompromitteerde patiënten. Ondanks recente vooruitgang in de diagnose en behandeling van ISI's blijft de mortaliteit door deze ziekten hoog. Het ontwikkelen van een nieuw antischimmelmedicijn is vaak tijdrovend en kostbaar, wat aangeeft dat het optimaliseren van de werkzaamheid van momenteel beschikbare medicijnen essentieel is.

In **Hoofdstuk 1** hebben we een overzicht gegeven van de huidige behandelingsmogelijkheden voor ISI's. Voor alle triazolen is een relatie tussen blootstelling en respons aangetoond. Desondanks worden clinici nog steeds geconfronteerd met verschillende problemen met betrekking tot veiligheid en/of (gebrek aan) werkzaamheid in de praktijk, die onder andere het gevolg zijn van sterk variërende blootstellingsniveaus aan het medicijn. Om deze kwesties beter aan te pakken, is het essentieel om de farmacokinetiek (PK) van deze triazool-geneesmiddelen te begrijpen. Dit proefschrift richt zich op de populatie PK-profielen van twee veelgebruikte triazool-antischimmelmiddelen, namelijk posaconazol en fluconazol, met speciale aandacht voor de orale absorptie en orale biobeschikbaarheid (F), om wetenschappelijk ondersteuning te leveren voor een optimale dosering.

Hoofdstuk 2 vat de bestaande kennis samen over posaconazol PK, farmacodynamiek (PD), toxiciteit, resistentie, klinische ervaring in speciale populaties en nieuwe therapeutische strategieën. Posaconazol vertoont een hoge variabiliteit in blootstelling tussen individuen, maar ook tussen de drie beschikbare formuleringen, tussen gezonde vrijwilligers en patiënten, en tussen verschillende patiëntenpopulaties. Ondanks toediening van een lagere dagelijkse dosis leveren de twee nieuwste formuleringen, namelijk het vertraagd vrijkomende tablet (DR-tablet) en de intraveneuze (IV) formulering, een hogere en stabielere blootstelling dan de orale suspensie. Om deze reden wordt het DR-tablet in de praktijk vaak verkozen boven de suspensie. Er ontbrak echter nog steeds een geïntegreerde analyse die de PK-verschillen van posaconazol tussen verschillende formuleringen en populaties beschrijft.

Om de in **Hoofdstuk 2** geïdentificeerde hiaten in onze kennis op te vullen, hebben we in **Hoofdstuk 3** eerst de populatie PK, inclusief de absolute F, van alle posaconazolformuleringen gekarakteriseerd, met een focus op gezonde vrijwilligers, om de mogelijk verstorende invloed van pathologische en klinische factoren te omzeilen. Voor de orale suspensie werden een invloed van voedsel op zowel F als absorptiesnelheid, evenals een dosis-non-lineariteit in F, gekwantificeerd, resulterend in lagere F onder nuchtere omstandigheden of bij toediening van een hogere dosis. Voedselinname verhoogt ook significant de F van het DR-tablet. De geteste comedicaties, waaronder maagzuurremmers, ranitidine, esomeprazol en metoclopramide, hadden geen statistisch significante invloed op de absorptie van het DR-tablet. Met een hogere en stabielere F werd de PK-superioriteit van de

posaconazol DR-tablet, in vergelijking met de orale suspensie, bevestigd. Toediening van het DR-tablet onder nuchtere omstandigheden resulteert echter in een lager dan verwachte F, wat suggereert dat toediening van het DR-tablet met voedsel moet worden overwogen om de absorptie te verbeteren en voldoende blootstelling te garanderen. Modelgebaseerde simulaties bij gezonde vrijwilligers laten zien dat bij toediening onder nuchtere omstandigheden meer dan 35% van de personen die de geadviseerde profylactische dosis van de orale suspensie of het DR-tablet ontvangen, een risico lopen op suboptimale blootstelling.

Omdat aanzienlijke verschillen tussen gezonde vrijwilligers en patiënten bekend zijn, hebben we in **Hoofdstuk 4** de geïntegreerde PK-analyse uitgebreid van de gezonde populatie naar (voornamelijk) hematologische patiënten. Bij patiënten is de F van het DR-tablet over het algemeen hoger dan de dosisafhankelijke niet-lineaire F van de orale suspensie en deze wordt niet beïnvloed door de geteste covariaten. Vijf klinische kenmerken bleken de F van de orale suspensie significant te verlagen, waaronder mucositis, diarree, toediening via een nasogastrische buis, en gelijktijdig gebruik van protonpompremmers of metoclopramide. Bovendien vertoonden patiënten een groter perifeer distributievolume en lagere intercompartimentale klaring in vergelijking met gezonde vrijwilligers, wat resulteert in verlaagde dalspiegels voor alle formuleringen. Patiënten met hypoalbuminemie vertoonden een lagere klaring (CL). Er werden geen raciale verschillen in PK gevonden tussen Chinese en blanke patiënten, wat suggereert dat Chinese patiënten geen aangepaste dosering nodig hebben. Hoewel het DR-tablet superieur is aan de orale suspensie, is de F lager dan eerder gerapporteerd, wat betekent dat de blootstelling bij toediening van dezelfde dosis niet gelijkwaardig is aan IV. Overschakelen naar IV of het verhogen van de dosis van het DR-tablet, gekoppeld aan therapeutische geneesmiddelmonitoring, moet daarom worden overwogen om optimale blootstelling te garanderen.

Posaconazol wordt het meest gebruikt voor schimmelprofylaxe. Fluconazol blijft het meest gebruikte antischimmelmiddel bij patiënten met verdachte of gediagnosticeerde gistinfecties zoals candidiasis. Het wordt gebruikt bij een breed scala aan individuen, onder wie patiënten met obesitas. Als een speciale populatie worden obese proefpersonen vaak uitgesloten van pre- of post-marketing klinische onderzoeken. Om ons kennisgebrek bij het voorschrijven van fluconazol bij obese patiënten te dichten, hebben we in **Hoofdstuk 5** een prospectieve PK-studie uitgevoerd bij obese proefpersonen en niet-obese gezonde proefpersonen die een semi-gelijktijdige dosis van de orale capsule van fluconazol en de IV formulering kregen. Op basis van de populatie PK had obesitas geen invloed op de F van de orale fluconazol capsule. Desondanks bleek dat deelnemers met een hoger totaal lichaamsgewicht zowel een hogere CL als een groter distributievolume hadden. Naast totaal lichaamsgewicht vonden we dat geslacht ook een statistisch significant invloed had op het distributievolume, wat resulteerde in een groter distributievolume bij mannen vergeleken met vrouwen van hetzelfde gewicht. Als gevolg hiervan hebben mannelijke proefpersonen met een hoog totaal lichaamsgewicht mogelijk

een verhoogde oplaaddoseringen nodig om te compenseren voor de langzamere accumulatie van het geneesmiddel naar steady-state. De veelgebruikte doseringsschema's voor oraal fluconazol laten een hoge variabiliteit in blootstelling zien, wat gepaard gaat met een verhoogde kans op onderdosering bij een groot deel van de obese populatie. Om de klinische implementatie van onze bevindingen te vergemakkelijken, hebben we doseringstabellen voorgesteld voor vrouwelijke en mannelijke proefpersonen met verschillende totale lichaamsgewichten.

List of publications

Chen L, Krekels EHJ, Dong Y, Chen L, Maertens JA, Blijlevens NMA, Knibbe CAJ, Brüggemann RJ. Meta-PK analysis of posaconazole upon dosing of oral suspension, delayed-release tablet, and intravenous infusion in patients versus healthy volunteers: impact of clinical characteristics and race. Int J Antimicrob Agents. 2023 Oct 6:106995.

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Curriculum vitae

Lu Chen (1993, Yan'an, China) started her academic journey in 2011, enrolling in a Bachelor of Science program in Pharmaceutical Science and a Bachelor of Economics in Finance at Xi'an Jiaotong University in China. In 2015, she successfully earned dual Bachelor's degrees in Science and Economics. For her graduation project, she undertook a project involving Monte Carlo simulations for her thesis, which introduced her to the field of pharmacometrics.

Following her undergraduate studies, Lu pursued a Master of Science program in Pharmaceutical Science at the same university and its first affiliated hospital in 2015, working under the supervision of Prof. Yalin Dong. During this period, she explored population pharmacokinetic modeling, the analytical technique of Liquid Chromatography-Mass Spectrometry (LC-MS), cell culture, and meta-analysis. Lu completed her Master's degree in Science in 2018 with honors.

In September 2018, Lu moved to The Netherlands and commenced her Ph.D. journey on a collaborative project between the Leiden Academic Center for Drug Research (LACDR) and the Radboud University Medical Center, under the supervision of Prof. C.A.J. Knibbe, Dr. E.H.J. Krekels, and Dr. R.J. Brüggemann. Her doctoral research was dedicated to optimizing antifungal dosing using population pharmacokinetics. Currently, Lu is actively engaged in the field of drug development at Certara Drug Development Solutions in Leiden.

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