No Dose Adjustment for Isavuconazole Based on Age or Sex

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Running Title: Age Sex and the Pharmacokinetics of Isavuconazole
ABSTRACT

This phase 1, open-label, single-dose, parallel-group study evaluated the pharmacokinetics (PK) of isavuconazole after a single oral dose of the prodrug isavuconazonium sulfate in healthy non-elderly (18–45 years) and elderly (≥65 years) males and females. Overall, 48 subjects were enrolled in the study (n = 12 each, non-elderly male and female and elderly male and female). All subjects received a single oral dose of 372 mg of isavuconazonium sulfate (equivalent to 200 mg isavuconazole). PK samples for isavuconazole plasma concentrations were collected pre-dose up to 336 h postdose. Data was analyzed using population pharmacokinetic (PPK) analysis. The resulting PPK model included two compartments with Weibull absorption function as well as inter-individual variability on clearance, inter-compartment clearance, volumes of central and peripheral compartments, and two Weibull absorption parameters, RA and KAMAX. The PPK analysis showed that elderly females had the highest exposure versus males (ratio of total area under the time-concentration curve [AUC], 138%; 90% confidence interval [CI]: 118%, 161%) and versus non-elderly females (ratio of AUC, 147%; 90% CI: 123%, 176%). Higher exposures in elderly females were not associated with significant toxicity or treatment-emergent adverse events, as measured in this study. No dose adjustments appear to be necessary based on either age group or sex even with an increase in exposure for elderly females.
INTRODUCTION

Pharmacotherapy can be a challenging aspect in the care of elderly patients as drug distribution, metabolism and renal elimination can all be affected by age group (1). There is an increased risk of drug-drug interactions and other adverse drug effects in the elderly compared with younger subjects, which can make the use of pharmacological interventions in the elderly more problematic (1). Invasive fungal disease (IFD) is a growing problem in the elderly because they are more likely to require transplantation or receive immunosuppressive drugs or chemotherapy for cancer than younger adults (2). The elderly are less able to cope with IFD and outcomes are frequently worse than in younger adults (2).

Triazole antifungal agents are frequently first-line agents for the prevention and treatment of IFD in older adults or immunocompromised patients with cancer or those requiring transplantation (3). Isavuconazonium sulfate is a water-soluble prodrug of the active triazole isavuconazole, which inhibits the sterol 14 alpha-demethylase, a microsomal P450 enzyme (P45014DM) that is essential for ergosterol biosynthesis in fungi (4, 5). Based on the results of phase 3 clinical trials (6, 7), isavuconazonium sulfate was approved by the U.S. Food and Drug Administration for the treatment of invasive aspergillosis (IA) and invasive mucormycosis in adults (8). It was also approved by the European Medicines Agency for the treatment of IA in adults and those with mucormycosis for whom amphotericin B is not appropriate (9).

It is crucial for the optimal clinical use to understand the pharmacokinetics (PK) of isavuconazole in various patient populations (10-13), including non-elderly and elderly male and female adults. The primary objectives of this study were to determine the PK profiles of isavuconazole after a single dose in healthy non-elderly and elderly adults and in male and female adult subjects and to determine if dose adjustment is needed based on either age group or sex.
RESULTS

Demographics and baseline characteristics. A total of 48 healthy adults were enrolled in the study including 12 female and 12 male non-elderly adults and 12 female and 12 male elderly adults (Table 1). The proportion of white subjects enrolled in the non-elderly group (13/24 [54.2%]) was similar to those enrolled in the elderly group (11/24 [45.8%]). The non-elderly group had a higher proportion of black or African Americans (7/24 [29.2%]) compared with the elderly group (1/24 [4.2%]). The mean weight and BMI were comparable between the non-elderly and elderly groups (Table 1). Across the age groups there were more white male subjects (17/24 [70.8%]) than white female subjects (7/24 [29.2%]). However, there were more black or African American (7/24 [29.2%]) and Asian (9/24 [37.5%]) female subjects across the age groups than their male counterparts (1/24 [4.2%] and 4/24 [16.7%], respectively). At least 25% of elderly subjects (three from each sex) were above 75 years of age.

Population pharmacokinetic model. Plasma concentrations of isavuconazole show a biexponential decline after the peak plasma concentration, with a prolonged terminal elimination phase (Figure 1). Initial population PK (PPK) model resulted in a two-compartment model, with unique clearance (CL) values for each group (elderly male, non-elderly male, elderly female and non-elderly female). Isavuconazole CL values were similar for non-elderly male subjects (CL ± SD: 1.94 ± 0.52 liters/h) and elderly male (2.04 ± 0.52 liters/h) whereas CL values differed between non-elderly and elderly females (2.13 ± 0.39 liters/h vs 1.44 ± 0.43 liters/h, respectively). The CL values are presented as box plots in Fig. 2. Therefore, in the modified base model, non-elderly and elderly male subjects were considered as a single group whereas non-elderly and elderly female subjects were treated as separate distinct groups. The PK model development process resulted in a modified base model that included two compartments with Weibull absorption function. The model had inter-individual variability on CL, inter-compartment clearance (Q), volumes of central and peripheral compartments (V2 and V3, respectively), and two Weibull absorption parameters,
RA and KAMAX. Modeling of isavuconazole PPK data then proceeded with an exploratory graphical inspection of potential covariate parameter relationship for the primary covariate of interest.

**Best model with covariates.** Following the development of the modified base model, covariates of interest were added in stepwise manner using the forward-addition/backward-elimination procedure. The only covariate statistically significant on $V_3$ was weight.

$$V_3 = \theta_4 \times [1 + \theta_9 \times (\text{WTKG} - 72)]$$

Where $\theta_4$ is the typical value of volume of distribution, $\theta_9$ is value of volume of distribution associated with changing weight, and WTKG is weight in kilograms. The diagnostics of the model fit (Supplementary Fig. 1) indicated an overall good fit of the model to the data. Typical population parameters, including covariate effects as well as most of the random variance parameters, were estimated with good precision. Plots of the normalized prediction distribution error (NPDE; Supplementary Fig. 2) demonstrated that the normality assumption was met and plots of NPDE versus time (independent variable) did not show any trend. The parameters for the best covariate model are presented in Table 2. All parameters were precisely estimated with percent relative standard errors ≤39% for the fixed effects and ≤40% for the random effects. Clearance shrinkage was 5%. The condition number of the two-compartment model was 65, indicating stability of the model.

Area under the curve was calculated using empirical Bayes estimates. Similar isavuconazole CL values were evident for male and non-elderly female subjects (Fig. 3). Elderly females had the highest exposure of the groups studied (ratio of elderly females versus males, 138%; 90% confidence interval [CI]: 118%, 161%; ratio of elderly females versus non-elderly females, 147%; 90% CI: 123%, 176%). Non-elderly females had similar area under the time-concentration curve (AUC) exposures compared with the combined male group (ratio, 94%; 90% CI: 80%, 109%).

**Safety analyses.** Overall, 15 subjects (31.3%) reported 19 treatment-emergent adverse
events (TEAEs) during the study (Table 3). Elderly females reported the highest number of TEAEs. Elderly females also reported the highest number of drug-related TEAEs (five TEAEs in four subjects [33.3%]) compared with elderly men (0), non-elderly females (two TEAEs in one subject [8.3%]) and non-elderly males (one TEAE in one subject [8.3%]). All TEAEs were mild in intensity. There were no serious adverse events and no deaths during the study. The most common MedDRA system organ class TEAE was gastrointestinal disorders occurring in two (16.7%) non-elderly males and three (25%) non-elderly females. There were no clinically meaningful changes from baseline for chemistry or hematology results. Overall, the mean vital sign measurements at baseline were similar to the mean vital signs after dosing with no clinically relevant changes. No subject experienced a clinically significant 12-lead ECG abnormality during the study.
DISCUSSION

The present study was designed to determine the effect of age group and sex on the PK profile of isavuconazole after a single 200 mg oral dose in healthy non-elderly and elderly male and female subjects. Data was analyzed by PPK. PPK analysis was performed to see if there was any potential bias in sampling time points that might affect the exposures of subjects and also to determine the effects of age and sex on the PK of isavuconazole. The PPK modeling showed that elderly female subjects had lower isavuconazole clearance values and higher exposure compared with the other groups in the study. However, the PK differences in elderly females were less than 1.5-fold as compared with other groups and were not considered clinically meaningful. One possible explanation for higher exposures in elderly females might be the predominance of Asian subjects. Data analyzed from phase 3 studies has shown that Asian subjects have higher exposures as compared with Caucasian subjects (10). Since the primary aim of this analysis was to see the effects of sex and age on the PK of isavuconazole, race was not analyzed and added as a covariate. The findings of our present study support the findings from two large phase 3 SECURE and VITAL clinical trials which showed that age group and sex did not affect the PK of isavuconazole (10, 12).

While there have been a number of studies on the PK and pharmacodynamics of other azoles [reviewed elsewhere (4, 14-18)], few have directly investigated the effect of age group or sex. One report showed that mean C\text{max} and AUC values for voriconazole were higher in young healthy females aged 18–45 years compared with young healthy men, but no significant differences were observed between healthy elderly men and elderly women (≥65 years) (14). However, in contrast to our results in healthy non-elderly and elderly subjects, voriconazole plasma concentrations were higher in elderly subjects compared with younger subjects (14). Another study showed that voriconazole exposure tended to increase with age and weight but the increase was not clinically meaningful (19). Furthermore, in one study age and sex was shown to have no clinically meaningful effects on the PK of
posaconazole (20, 21). None of these studies of other azoles indicated that adjustment of dose was required on the basis of age group or sex of the recipients.

Isavuconazole given as a single dose was safe and well tolerated in elderly subjects as well as in non-elderly subjects. TEAEs were reported more frequently in the elderly female subject group, however, all TEAEs reported were mild in intensity and no clinically relevant effect on vital signs or physical examination findings were observed in this study. Although PPK analysis showed that elderly female subjects had lower CL values and higher exposure compared with the other groups of subjects investigated, higher exposures in elderly females were not associated with significant toxicity, as measured in this study. Therefore, no dose adjustment of isavuconazole appears to be necessary based on either the age group or sex of individuals.
MATERIALS AND METHODS

Study. This was a phase 1, open-label, parallel group, single dose study to assess the PK of isavuconazole in healthy male and female adults (ClinicalTrials.gov registration no. NCT01657890). The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. An institutional review board at the study center approved the protocol and all amendments. All subjects provided written informed consent prior to enrollment.

Subjects. Subjects were eligible for the study if they were healthy non-elderly adults aged between 18 and 45 years or were healthy elderly adults aged ≥65 years, had a calculated creatinine clearance within the age-appropriate normal range or, if abnormal, the abnormality was not clinically significant. Additionally, body weight and body mass index (BMI) of eligible subjects must have been at least 45 kg and between 18 and 32 kg/m², respectively, 12-lead electrocardiograph (ECG) was to be normal at screening and on day –1 or, if abnormal, the abnormality was not clinically significant, as determined by the investigator. Aspartate aminotransferase, alanine aminotransferase, and total bilirubin were to be within the normal reference range.

Exclusion criteria included non-elderly subjects with any clinically significant disease history of pulmonary, gastrointestinal, cardiovascular, hepatic, respiratory, neurological, psychiatric, renal, genitourinary, endocrine, metabolic, dermatologic, immunologic, hematologic, inflammation, or malignancy excluding non-melanoma skin cancer. Other exclusion criteria included the following: history of cardiac disorders; viral, bacterial or fungal infection 7 days prior to baseline visit or vaccination 30 days prior to baseline visit; hepatitis B, hepatitis C or HIV positivity; and/or a medical or surgical condition that may have interfered with the absorption, distribution, metabolism, or excretion of isavuconazole.

Study design. All subjects received a single dose of 372 mg of isavuconazonium sulfate, corresponding to 200 mg of isavuconazole, on day 1, after fasting for approximately 10 h prior to dosing. Subjects attended the study center from day –1 to day 4 and returned to the...
center for outpatient assessments on days 6, 8, 11, 13, and 15. Serial blood samples for isavuconazole PK were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 120, 168, 228, 240, and 336 h postdose.

Safety assessments. The safety analysis set consisted of all participants who had one oral dose of isavuconazole. Safety assessments included an evaluation of the incidence, nature and severity of adverse events, TEAEs, drug-related TEAEs, ECG and vital sign measurements including 12-lead ECG.

Data analysis. Non-compartmental analysis was performed on the PK data, which is not presented in this manuscript. However, some of the parameters might not have been reliable due to insufficient sampling time in the elimination phase. Therefore, PPK was performed to estimate parameters with reliability. A total of 882 concentrations from 48 subjects were used for modeling. PPK modeling was performed using the concentration-time data in both elderly male and female and non-elderly male and female subjects using non-linear mixed-effects modeling with the software program NONMEM (version 7.2; GloboMax LLC, Hanover, MD). The first-order conditional estimation methods in NONMEM were employed for all model runs. Model selection was driven by data and based on various goodness-of-fit criteria, which included visual inspection of diagnostic scatter plots (observed versus individual predicted concentration), successful convergence of the minimization routine with at least two significant digits in parameter estimates, precision of parameter estimates, and the minimum objective function value and the number of estimated parameters.

Structural pharmacokinetic model. A variety of linear compartmental models were explored to describe total isavuconazole concentration-time data. The base PPK model included two compartments, with either simple first-order absorption models or the Weibull absorption model. All random effects were treated as log-normally distributed. The In-In transformations of both the model and the data were used to stabilize the residual variance. The residual variance was finally modeled as additive in nature. The models were coded using NONMEM subroutines for prediction of PPK parameters. Initially, different age/sex
group (non-elderly males, elderly males, non-elderly females, and elderly females) were built directly into the base model by allowing each group to have their own unique population mean CL values since aim was to determine if PK was different based on age or sex.

**Pharmacokinetic model with covariates.** Following development of the base structural PPK model, a covariate analysis was conducted to determine stepwise covariate modeling was performed in PSN (psn-sourceforge.net), by forward-inclusion and backward-elimination steps. In the forward inclusion step, covariates (age, weight, BMI) were added to the model one at a time, using a $P$-value of 0.01 for entry into the model. Univariate analysis of all specified covariate-parameter relationships was explored. The best covariate was added to the model and the univariate step was repeated with remaining covariates. This process was continued until no more significant covariates were left to be added to the model. In the backward-elimination step covariates were removed one at a time using a $P$-value of 0.01 for retention in the model. The process was continued until all remaining covariates were significant. Total AUC at steady state for individual subjects was calculated using the standard formula \( \text{AUC} = F \times \text{Dose}/\text{CL} \), where $F$ is bioavailability and CL is clearance) based on the individual parameter estimates from the best covariate model.

**Statistical analysis of AUC**

To assess the effect of elderly/nonelderly females vs males, an analysis of variance with log transformed AUC was conducted. The ratio of geometric means and the corresponding 90% confidence intervals were provided.

**Model validation.** For the best covariate model, population and individual PK parameters were estimated and the precision of the population model parameters (e.g., asymptotic standard errors or bootstrap 95% CIs were generated. Nonparametric bootstrapping, using 500 replications, was used to provide validation of the model parameter estimated. The NPDE data were also plotted to evaluate the best model.

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DATA SHARING STATEMENT
Access to anonymized individual participant level data will not be provided for this trial as it meets one or more of the exceptions described on www.clinicalstudydatarequest.com under "Sponsor Specific Details for Astellas."
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**Figure Legends**

**FIG 1** Mean ± standard deviation plasma concentration of isavuconazole by age group and sex in the pharmacokinetic analysis set. Inset shows expanded 0–48 h interval.

**FIG 2** Isavuconazole clearance values for the different groups based on age and sex in subjects from the pharmacokinetic analysis set. Boxes represent median, 25th and 75th percentiles, whiskers represent 1.5 × the interquartile range, solid gray circles are means, and open circles are outliers.

CL, clearance.

**FIG 3** Isavuconazole clearance values from the two-compartment model in the pharmacokinetic analysis set. Boxes represent median, 25th and 75th percentiles, whiskers represent 1.5 × the interquartile range, solid gray circles are means, and open circles are outliers.

CL, clearance.
TABLE 1 Participant demographics

| Parameter          | Non-elderly |   | Elderly |   |
|--------------------|-------------|---|---------|---|
|                    | Male (N = 12) | Female (N = 12) | Male (N = 12) | Female (N = 12) |
| Ethnicity, n (%)   |             |             |         |   |
| White              | 9 (75)      | 4 (33.3)    | 8 (66.7)  | 3 (25.0)   |
| Black or African   | 1 (8.3)     | 6 (50.0)    | 0         | 1 (8.3)    |
| American Indian    | 1 (8.3)     | 0           | 4 (33.3)  | 8 (66.7)   |
| Other              | 1 (8.3)     | 1 (8.3)     | 0         | 0          |
| Age, mean ± SD     | 30.3 ± 7.59 | 29.5 ± 6.45 | 70.9 ± 5.74 | 71.5 ± 5.50 |
| Range              | 19–42       | 22–45       | 65–85     | 66–84      |
| Weight, mean kg ± SD | 80.17 ± 12.90 | 70.01 ± 10.49 | 77.88 ± 11.58 | 61.03 ± 8.71 |
| Range              | 57.0–105.7  | 56.3–86.5   | 59.1–94.1 | 51.7–80.0 |
| BMI, mean kg/m² ± SD | 26.44 ± 3.32 | 26.17 ± 3.47 | 25.98 ± 2.36 | 24.52 ± 3.28 |
| Range              | 20.2–31.7   | 19.6–30.9   | 22.5–29.8 | 19.7–30.0 |

BMI, body mass index; SD, standard deviation.
| Parameter | Value | % RSE | Bootstrap mean | Bootstrap 95% CI |
|-----------|-------|-------|----------------|-----------------|
| $\theta_1$ (CL, male), liters/h | 1.99 | 6 | 1.98 | 1.75–2.23 |
| $\theta_2$ (CL, non-elderly female), liters/h | 2.13 | 6 | 2.13 | 1.87–2.38 |
| $\theta_3$ (CL, elderly female), liters/h | 1.44 | 10 | 1.45 | 1.17–1.71 |
| $\theta_4$ (V2), ml | 9,220 | 14 | 9,140 | 3,993–14,450 |
| $\theta_5$ (Q), ml/h | 22,200 | 4 | 22,190 | 20,252–24,092 |
| $\theta_6$ (V3), ml | 263,000 | 5 | 264,231 | 234,000–292,835 |
| $\theta_7$ (RA) | 0.664 | 6 | 0.661 | 0.574–0.735 |
| $\theta_8$ (GAM1) | 4.75 | 10 | 4.77 | 3.62–5.87 |
| $\theta_9$ (KAMAX), h$^{-1}$ | 0.426 | 6 | 0.42 | 0.368–0.482 |
| $\theta_{10}$ V3 WTKG, Male | 0.0212 | 10 | 0.021 | 0.0141–0.028 |
| $\theta_{11}$ V3 WTKG, non-elderly female | 0.443 | 39 | 0.458 | 0.1–0.786 |
| $\theta_{12}$ V3 WTKG elderly female | 0.654 | 23 | 0.663 | 0.204–1.10 |

CI, confidence interval; CL, clearance; V2, volume of central peripheral compartment; V3, volume of peripheral compartment; Q, intercompartmental clearance; WTKG, body weight; GAM1, KAMAX, RA, Weibull absorption parameters.
| System Order Class preferred term, n (%) | Non-elderly | Elderly |
|----------------------------------------|-------------|---------|
| Overall                                | Male (N = 12) | Female (N = 12) | Male (N = 12) | Female (N = 12) |
| Abdominal pain                          | 1 (8.3)     | 0        | 0            | 0              |
| Constipation                            | 0           | 0        | 0            | 1 (8.3)        |
| Diarrhea                                | 1 (8.3)     | 0        | 0            | 0              |
| Hematochezia                            | 0           | 0        | 0            | 1 (8.3)        |
| Nausea                                  | 0           | 0        | 0            | 1 (8.3)        |
| Dizziness                               | 1 (8.3)     | 0        | 0            | 1 (8.3)        |
| Headache                                | 0           | 0        | 0            | 2 (16.7)       |
| Presyncope                              | 0           | 0        | 1 (8.3)      | 0              |
| Influenza like illness                  | 1 (8.3)     | 0        | 0            | 0              |
| Infusion site extravasation             | 0           | 0        | 1 (8.3)      | 0              |
| Tenderness                              | 0           | 0        | 0            | 1 (8.3)        |
| Skin laceration                         | 0           | 1 (8.3)  | 0            | 0              |
| Thermal burn                            | 0           | 0        | 0            | 1 (8.3)        |
| Nasopharyngitis                         | 0           | 1 (8.3)  | 0            | 0              |
| Vulvovaginal infection                  | 0           | 1 (8.3)  | 0            | 0              |
| Hepatic enzyme increased                | 0           | 0        | 0            | 1 (8.3)        |
| Back pain                               | 0           | 0        | 0            | 1 (8.3)        |
