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APPLICATION NUMBER

NDA 21-632

NDA 21-948

**Clinical Pharmacology and Biopharmaceutics
Review**

Office of Clinical Pharmacology and Biopharmaceutics Review

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| NDA | 21-632 |
| Drug Product; Brand® | Anidulafungin for injection, 50 mg; ERAXIST™ |
| Submission Date | January 24, 2006 |
| Applicant | Pfizer |
| Clinical Division | DSPTP |
| OCPB Division | DCP4 |
| Type of Submission | NDA resubmission |
| Reviewer | Dakshina M. Chilukuri, Ph.D. |
| Team Leader | Philip M. Colangelo, Pharm D., Ph.D. |
| Review Date | February 15, 2006 |

I. Executive Summary

The sponsor submitted revised labeling information in this submission and this revised label is a combined label for esophageal candidiasis and invasive candidiasis/candidemia. This revised label was reviewed in NDA 21-948 and the corresponding clinical pharmacology review was DFSed on 02/14/2006. No additional information was submitted as part of this current submission and thus, a review for this submission is not necessary. Also, please refer to the DFSed review dated 11/18/2005 for additional information regarding NDA 21-632.

Dakshina M. Chilukuri, Ph.D. _____
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

Initialed by Philip Colangelo, Pharm D., Ph.D. _____
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Office of Clinical Pharmacology
cc: NDA 21-632 and CDR (Biopharm)

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Dakshina Chilukuri
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Phil Colangelo
2/16/2006 11:26:07 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics Review

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| NDA | 21-948 |
| Drug Product; Brand[®] | Anidulafungin for injection, 100 mg; Eraxis[™] |
| Submission Date | August 18, 2005 |
| Applicant | Pfizer |
| Clinical Division | DSPTP |
| OCP Division | DCP4 |
| Type of Submission | NDA submission |
| Reviewer | Dakshina M. Chilukuri, Ph.D. |
| Team Leader | Philip M. Colangelo, Pharm D., Ph.D. |
| Review Date | February 02, 2006 |

I. Executive Summary

The applicant is seeking approval of Anidulafungin, an antifungal agent belonging to the Echinocandin class for intravenous (IV) administration in NDA 21-948. The proposed indication is treatment of candidemia and other forms of invasive candidiasis. The proposed dosage regimen is a loading dose of 200 mg on the first day, followed by a maintenance dose of 100 mg IV once daily for duration of treatment based on the patients' response.

In NDA 21-632, the applicant requested approval of anidulafungin (100 mg loading IV dose followed by 50 mg maintenance doses for 14-21 days) for the treatment of esophageal candidiasis. The Division of Special Pathogen and Transplant Products (DSPTP) issued on November 24, 2006, an approvable letter requesting labeling revisions. In the current submission, the sponsor has provided safety and efficacy data to support approval of anidulafungin in the treatment of candidemia and other forms of invasive candidiasis. The sponsor has also submitted a combined label for both indications, namely, esophageal candidiasis and candidemia and other forms of invasive candidiasis.

The pharmacokinetics (PK) of anidulafungin were previously submitted as part of NDA 21-632. A population pharmacokinetic model was developed using data from Phase 2-3 studies of IV anidulafungin, and reported in NDA 21-632. The original analysis included 600 anidulafungin concentrations from 225 patients across 4 completed or ongoing Phase 2 and 3 clinical trials (VER002-4, VER002-6, VER002-7, and VER002-11).

Since the submission of the original NDA 21-632, additional patient data were collected and examined on the population pharmacokinetic model. The developed model presented in the original submission contained only 9 patients from clinical studies VER002-7 and VER002-11. These studies were completed, and the entire sets of pharmacokinetic data were applied to the model. The dosage regimen in VER002-7 was IV anidulafungin 200 mg loading dose followed by IV AmBisome[®] at a dose of up to 5 mg/kg/day on Day 1; IV anidulafungin 100 mg followed by IV AmBisome[®] at a dose of up to 5 mg/kg/day on Day 2 through the end of treatment. Investigators were permitted to reduce the dose of AmBisome[®], if deemed necessary because of toxicity. The dosage regimen in VER002-11 was IV anidulafungin 100 mg on Day 1, IV anidulafungin 50 mg daily on Day 2 through

end of treatment. Thus the final population PK model was developed using data from patients receiving maintenance doses of 50 and 100 mg/day IV anidulafungin following administration of loading doses of 100 and 200 mg/kg, respectively.

The pharmacokinetic data collected since the original submission continued to support the developed model. The data from VER002-7 included data from the previous studies and all available data from this study for a total of 660 concentrations from 245 patients. The population pharmacokinetic model was re-run using this data. The data were well described by the anidulafungin population pharmacokinetic model. There was little difference between parameters from the previously reported model and the model obtained by fitting the appended data file. All parameter estimates were within 15% of the original values. The distribution of the post-hoc clearance (CL) estimates between the two data sets was also similar.

The data appended to the population pharmacokinetic data file included data from the previous studies and all available data from Clinical Study VER002-11 for a total of 819 concentrations from 262 patients. There was little difference between parameters from the previously reported model and the model obtained by fitting the appended data file. All parameter estimates were within 20% of the original values. Patients in VER002-11 had azole-refractory mucosal candidiasis. Post-hoc estimates of CL from patients in VER002-11 were compared to patients from other studies (VER002-4 [esophageal candidiasis], VER002-6 [invasive candidiasis], and VER002-7 [invasive aspergillosis]) and no differences were observed in CL.

No outstanding clinical pharmacology issues were identified with anidulafungin in this current NDA submission.

A. Recommendations

The Office of Clinical Pharmacology /Division of Clinical Pharmacology 4 has reviewed the clinical pharmacology information included in this resubmission of NDA 21-948 for Anidulafungin and the reviewer has deemed this information to be acceptable. The Human Pharmacokinetics and Bioavailability Section of NDA 21-948 has met the requirements of the 21 CFR.

B. Phase IV Commitments

There are no clinical pharmacology/biopharmaceutics Phase IV commitments.

Dakshina M. Chilukuri, Ph.D. _____
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

Initialed by Philip Colangelo, Pharm D., Ph.D. _____

cc: NDA 21-948 and CDR (Biopharm)

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Appendix-B: Summary of population PK analysis

Background:

A population pharmacokinetic model was developed using data from Phase 2-3 studies of IV anidulafungin, and reported in original NDA 21-632. This population PK report was reviewed by Dr. Yaning Wang. As part of the ongoing anidulafungin development program, data from patients were collected in clinical studies and used to further validate the model. The results of these additional analyses are reported here.

Summary of population PK Model developed previously in NDA 21-632:

A population pharmacokinetic model for IV anidulafungin was presented in original NDA 21-632. Please see the review by Dr. Yaning Wang for additional information. The primary purpose of the analysis was to:

1. develop a population pharmacokinetic model to quantitate the pharmacokinetic parameters in patients with fungal infections,
2. determine the significance of possible covariates on the population pharmacokinetic parameters,
3. estimate the inter-patient variability of the anidulafungin pharmacokinetic parameters and the random residual error.

The original analysis included 600 anidulafungin concentrations from 225 patients across 4 completed or ongoing Phase 2 and 3 clinical trials (VER002-4, VER002-6, VER002-7, and VER002-11). Patients in VER002-4 (n = 129) had esophageal candidiasis and received 50 mg/day of anidulafungin for 14 to 21 days. Patients in VER002-6 (n = 87) had invasive candidiasis and received 14 to 42 days of anidulafungin treatment (50, 75, or 100 mg/day). Patients in VER002-7 (n = 7) had invasive aspergillosis and received up to 90 days of anidulafungin (100 mg/day) in combination with AmBisome® (liposomal amphotericin B). Patients in VER002-11 (n = 2) had fluconazole refractory mucosal candidiasis and received a 50 mg/day anidulafungin for 14 to 21 days. All plasma concentrations that were obtained from these studies were at steady-state, after at least three doses of anidulafungin (including a loading dose). Mixed-effects models were evaluated using the First Order (FO) and First Order Conditional Estimation with Interaction (FOCEI) maximum likelihood estimation in the NONMEM program (Version V, Level 1.1) and NM-TRAN pre-processor. Potential covariates examined on the model included demography (age, gender, weight, and ethnicity), study protocol, concomitant medications, HIV status, and the use of either water or ethanol as a diluent for drug product reconstitution.

A description of the final population model is shown in Table 6.3.7A. A two-compartment model with first order elimination provided the best fit of the data. In the base model, the CL, V_1 , and V_{ss} were estimated to be 0.946 L/h, 9.97 L, and 33.2 L, respectively. The pharmacokinetic parameters determined from the population analysis were similar to the parameters determined in the phase 1 studies. In the statistical model structure, inter-patient variability was only supported on the CL parameter, and this parameter was found to be influenced by patient weight and gender. Weight was also determined to be a predictor of V_1 . Inter-patient variability on CL was estimated to be

28%, and although covariates (gender, weight, and being in VER002-6) were identified as sources of variability in CL, together they accounted for inter-patient variability of less than 20%.

The population pharmacokinetic analysis showed no significant pharmacokinetic drug interactions for patients who received concomitant medications that were deemed to be drugs with a high potential for drug interactions. Medications that were administered while patients were on anidulafungin therapy were grouped as P450 metabolic substrates, inducers, and inhibitors. Patients were categorized for the presence or absence of each of these groups and these categories were explored on the model. Additionally, the presence or absence of rifampin was tested on the model as more than 10% of the sampled population received rifampin or a rifampin-containing product concomitantly. Rifampin is an important signal for potential drug interactions because it is a potent microsomal P450 enzyme inducer. None of the concomitant medications categories were statistically significant covariates on the population pharmacokinetic model; patients who received concomitant metabolic inhibitors, metabolic inducers, or rifampin had similar pharmacokinetic parameters as patients who did not receive these drugs (Figure 6.3.7A).

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TABLE 6.3.7A. INTRAVENOUS ANIDULAFUNGIN POPULATION PHARMACOKINETIC MODEL PARAMETER ESTIMATES

| Anidulafungin Final Model Parameter Estimates – FOCEI Method | | |
|--|---|---------------------------|
| Structural Model and Inter-patient Variance Parameters | | |
| Parameter | Typical Value (%RSE*) | Inter-patient %CV (%RSE*) |
| CL (L/h) | CL = $\theta_1 + (WT - MWT) * \theta_5 +$ GENDER * $\theta_6 +$ STUDY * θ_7 | 28.0% (17.6%) |
| θ_1 | 0.768 (3.80%) | - |
| θ_5 | 0.00417 (26.9%) | - |
| θ_6 | 0.166 (25.4%) | - |
| θ_7 | 0.278 (20.8%) | - |
| V_1 (L/kg) | $V_1 = \theta_2 * WT$ | NS |
| θ_2 | 0.215 (20.3%) | - |
| Q (L/h) | Q = θ_3 | NS |
| θ_3 | 20.3 (16.7%) | - |
| V_2 (L) | $V_2 = \theta_4$ | NS |
| θ_4 | 19.6 (15.1%) | - |
| V_{ss} (L) | 33.4** | 14.3%*** |
| $T_{1/2}$ (h) | 25.6** | 29.1%*** |
| Parameter | Residual Error Estimate (%RSE*) | |
| σ^2_{prop} | %CV = 24.0% (9.69%) | NA |

*%RSE: percent relative standard error of the estimate = SE/parameter estimate * 100 (for variability terms this is the %RSE of the variance estimate)

**Calculated from individual parameter values: $T_{1/2} = \text{Log}(2) / (0.5 * ((K + K_{12} + K_{21}) - \text{SQRT}((K + K_{12} + K_{21}) - (4 * K * K_{21}))))$, $V_{ss} = V_1 + V_2$

***Calculated as (Standard Deviation / Mean) * 100

Abbreviations: FOCEI = first order conditional estimation with interaction, CL = clearance, V_1 = central volume of distribution, Q = intercompartmental clearance, V_2 = peripheral volume of distribution, V_{ss} = volume of distribution at steady-state, $T_{1/2}$ = terminal phase half-life, σ^2_{prop} = proportional component of the residual error model, NS = Not Supported in Model, NA = Not Applicable, WT = weight (kg), MWT = 60 kg, GENDER = 1 for males and 0 for females; STUDY = 1 for VER002-6 and 0 for all other studies
Table from GloboMax Report RAVES00100, submitted in Original NDA 21-632.

Current Submission: Additional Patient Data to Support the IV Anidulafungin Pharmacokinetic Model

Since the submission of the original NDA 21-632, additional patient data were collected and examined on the population pharmacokinetic model. The developed model presented in the original submission contained only 9 patients from clinical studies VER002-7 and VER002-11. These studies were completed, and the entire sets of pharmacokinetic data were applied to the model. The dosage regimen in VER002-7 was IV anidulafungin 200 mg loading dose followed by IV AmBisome[®] at a dose of up to 5 mg/kg/day on Day 1; IV anidulafungin 100 mg followed by IV AmBisome[®] at a dose of up to 5 mg/kg/day on Day 2 through the end of treatment. Investigators were permitted to reduce the dose of AmBisome[®], if deemed necessary because of toxicity. The dosage regimen in VER002-11 was IV anidulafungin 100 mg on Day 1, IV anidulafungin 50 mg daily on Day 2 through end of treatment. Thus the final population PK model was developed using data from patients receiving maintenance doses of 50 and 100 mg/day IV anidulafungin following administration of loading doses of 100 and 200 mg/kg, respectively.

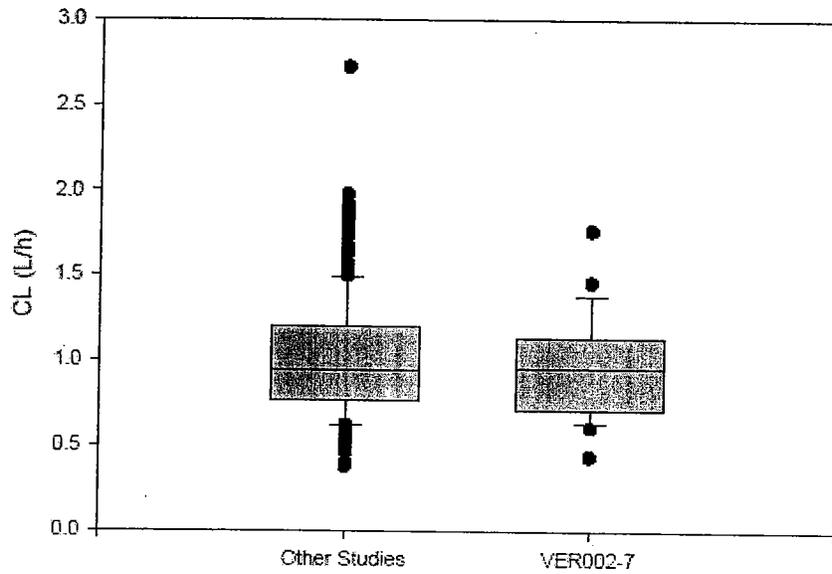
The pharmacokinetic data collected since the original submission continued to support the developed model. The appended data file from VER002-7 included data from the previous studies and all available data from this study for a total of 660 concentrations from 245 patients. The population pharmacokinetic model was re-run using this appended data file (NONMEM, first order conditional estimate method with interactions [FOCEI]). The data were well described by the anidulafungin population pharmacokinetic model. There was little difference between parameters from the previously reported model and the model obtained by fitting the appended data file as shown in Table 6.3.7B. All parameter estimates were within 15% of the original values. Differences between estimates of the non-covariate dependent parameters were even smaller (<7%). The distribution of the post-hoc CL estimates between the two data sets was also similar.

Unlike previous studies, patients in VER002-7 had invasive aspergillosis and were treated concomitantly with AmBisome[®] (liposomal preparation of amphotericin B). Post-hoc estimates of CL from patients in VER002-7 were compared to patients from other studies (VER002-4, VER002-6, and VER002-11). No differences were observed in CL (Figure 6.3.7B). Patients with invasive aspergillosis receiving AmBisome[®] had similar pharmacokinetics as patients with esophageal or invasive candidiasis who did not receive daily AmBisome[®]. The data appended to the population pharmacokinetic data file included data from the previous studies and all available data from Clinical Study VER002-11 for a total of 819 concentrations from 262 patients. The data were well described by the anidulafungin population pharmacokinetic model. There was little difference between parameters from the previously reported model and the model obtained by fitting the appended data file as shown in Table 6.3.7B. All parameter estimates were within 20% of the original values.

Patients in VER002-11 had azole-refractory mucosal candidiasis. Post-hoc estimates of CL from patients in VER002-11 were compared to patients from other studies (VER002-4 [esophageal candidiasis], VER002-6 [invasive candidiasis], and VER002-7 [invasive aspergillosis]) and no differences were observed in CL. The additional data collected from studies VER002-7 and VER002-11 are consistent with data presented in original NDA 21-632.

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FIGURE 6.3.7B. COMPARISON OF ANIDULAFUNGIN CLEARANCE (CL) BETWEEN PATIENTS WITH ASPERGILLOSIS RECEIVING AMPHOTERICIN TO PATIENTS FROM OTHER STUDIES.



* Data from clinical study VER002-7 submitted with the Anidulafungin EC Amendment, VER002-7 Clinical Study Report.

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TABLE 6.3.7B. COMPARISON OF ANIDULAFUNGIN POPULATION PHARMACOKINETIC MODEL PARAMETER ESTIMATES (ORIGINAL DATA FILE VERSUS APPENDED DATA FILES)

| Parameter | Typical Value (%RSE ^a) | | | Inter-patient %CV (%RSE ^b) | | |
|---------------------------------|--|------------------------|-------------------------|--|------------------------|-------------------------|
| | Original Data | Appended Data VER002-7 | Appended Data VER002-11 | Original Data | Appended Data VER002-7 | Appended Data VER002-11 |
| CL (L/h) | CL = $\theta_1 + (WT - MWT) * \theta_5 + GENDER * \theta_6 + STUDY * \theta_7$ | | | 28.0% (17.6%) | 27.3% (17.5%) | 27.2% (16.2%) |
| θ_1 | 0.768 (3.80%) | 0.768 (3.49%) | 0.777 (3.31%) | - | - | - |
| θ_5 | 0.00417 (26.9%) | 0.00439 (22.0%) | 0.00461 (21.6%) | - | - | - |
| θ_6 | 0.166 (25.4%) | 0.186 (21.3%) | 0.183 (20.9%) | - | - | - |
| θ_7 | 0.278 (20.8%) | 0.265 (20.4%) | 0.256 (20.7%) | - | - | - |
| V1 (L) | V1 = $\theta_2 * WT$ | | | NS | NS | NS |
| θ_2 | 0.215 (20.3%) | 0.230 (19.0%) | 0.170 (24.0%) | - | - | - |
| Q (L/h) | Q = θ_3 | | | NS | NS | NS |
| θ_3 | 20.3 (16.7%) | 19.4 (17.1%) | 21.6 (10.5%) | - | - | - |
| V2 (L) | V2 = θ_4 | | | NS | NS | NS |
| θ_4 | 19.6 (15.1%) | 19.2 (15.7%) | 23.5 (11.0%) | - | - | - |
| V _{ss} (L) | 33.4 ^b | 34.1 ^b | 34.6 ^b | 14.3% ^c | 14.8% ^c | 10.0% ^c |
| t _{1/2} (h) | 25.6 ^b | 26.0 ^b | 26.5 ^b | 29.1% ^c | 28.7% ^c | 27.3% ^c |
| Residual Error Parameter | | | | | | |
| σ^2_{prop} | 24.0% (9.69%) | 23.6% (9.12%) | 24.0% (9.79%) | | | |

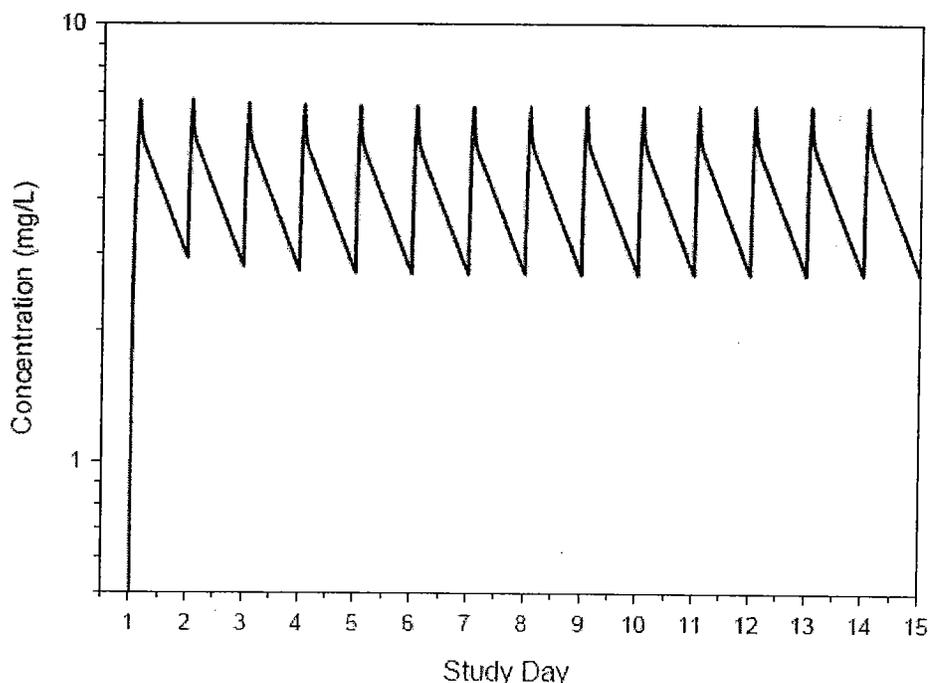
a: %RSE: percent relative SE of the estimate = SE/parameter estimate * 100 (for variability terms this is the %RSE of the variance estimate)
b: Calculated from individual parameter values
c: Calculated as (Standard Deviation / Mean) * 100
Abbreviations: FOCEI = first order conditional estimation with interaction, CL = clearance, V₁ = central volume of distribution, Q = intercompartmental clearance, V₂ = peripheral volume of distribution, V_{ss} = volume of distribution at steady-state, t_{1/2} = terminal phase half-life, σ^2_{prop} = proportional component of the residual error model, NS = Not Supported in Model, NA = Not Applicable, WT = weight (kg), MWT = 60 kg, GENDER = 1 for males and 0 for females; STUDY = 1 for VER002-6 and 0 for all other studies.
Reports contained in Original NDA 21-632 and Anidulafungin EC Amendment.

Anidulafungin Concentrations and Parameters in Patients: 100 mg/day IV Anidulafungin

Original NDA 21-632 summarized the anidulafungin plasma pharmacokinetics for patients receiving 50 mg/day IV anidulafungin. Concentrations and drug exposures were estimated for patients using the population pharmacokinetic model. This model was developed using data from patients receiving 50 and 100 mg/day IV anidulafungin. To support the indication for candidemia and other forms of invasive candidiasis, concentrations and parameters were estimated for a typical patient with invasive candidiasis (VER002-6) receiving 100 mg/day. The anidulafungin plasma concentration-time curve for this typical female patient weighing 60 kg is shown in Figure 6.3.7C. A comparison of concentration and exposure parameters between the 50 and 100 mg/day dosages is shown in Table 6.3.7C.

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FIGURE 6.3.7C. ANIDULAFUNGIN PLASMA CONCENTRATION-TIME CURVE FOR A TYPICAL PATIENT* RECEIVING 100 MG/DAY IV ANIDULAFUNGIN



* Simulation of a typical female patient with invasive candidiasis in clinical study VER002-6, weighing 60 kg: CL = 1.05 L/h, V1 = 12.9 L, Q = 20.3 L/h, V2 = 19.6 L. Dosage of 100 mg/day IV anidulafungin (with loading dose). Model from **L** **J** Report RAVES00100, submitted in original NDA 21-632.

TABLE 6.3.7C. COMPARISON OF CONCENTRATION AND EXPOSURE PARAMETERS FOR A TYPICAL PATIENT* RECEIVING EITHER 50 OR 100 MG/DAY

| Parameter | Dosage | |
|---------------------|-----------|------------|
| | 50 mg/day | 100 mg/day |
| C_{max} (mg/L) | 3.7 | 6.5 |
| C_{min} (mg/L) | 1.3 | 2.7 |
| AUC_{SS} (mg·h/L) | 47.7 | 95.4 |

* Simulation of a typical female with invasive candidiasis weighing 60 kg: CL=1.05 L/h (0.0175 L/h/kg), V1=12.9 L, Q=20.3 L/h, V2=19.6 L, V_{SS} =32.5 (0.542 L/kg), $t_{1/2}$ =21.9. Steady-state parameters are max. concentration (C_{max}), min. concentration (C_{min}), and AUC_{SS} . Dosages: 50 mg/day and 100 mg/day (with loading dose), infusion rate of 1 mg/min. Model submitted in Original NDA 21-632.

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/s/

Dakshina Chilukuri
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BIOPHARMACEUTICS

Phil Colangelo
2/14/2006 04:56:54 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics Review

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| NDA | 21-632 |
| Drug Product; Brand[®] | Anidulafungin for injection, 50 mg; τ \downarrow |
| Submission Date | May 27, 2005 |
| Applicant | Vicuron Pharmaceuticals Inc. |
| Clinical Division | DSPTP |
| OCPB Division | DCPB4 |
| Type of Submission | NDA resubmission |
| Reviewer | Dakshina M. Chilukuri, Ph.D. |
| Team Leader | Philip M. Colangelo, Pharm D., Ph.D. |
| Review Date | November 15, 2005 |

I. Executive Summary

The applicant is seeking approval of Anidulafungin, an antifungal agent belonging to the Echinocandin class for intravenous (IV) administration in NDA 21-632. The proposed indication is treatment of esophageal candidiasis. The proposed dosage regimen is a loading dose of 100 mg on the first day, followed by a maintenance dose of 50 mg IV once daily for 14-21 days of treatment.

This is a resubmission of the NDA that was submitted in April 2003, for which, an approvable letter (AE) was issued in May 2004. In the previous submission, several deficiencies were identified, which included the need to characterize the safety of anidulafungin and also to better demonstration of the risk-benefit ratio for the use of anidulafungin in the treatment of esophageal candidiasis. In this submission, the sponsor has provided additional safety and efficacy data to support approval of anidulafungin in the treatment of esophageal candidiasis.

The Pharmacokinetics (PK) of anidulafungin were previously submitted as part of the original submission of NDA 21-632 and no additional clinical pharmacology information was requested by FDA in the AE letter mentioned above. However, in this resubmission, the applicant submitted PK drug interaction studies with voriconazole and tacrolimus. Also, the results of a PK study in pediatric patients between 2-17 years of age were submitted.

Based on the review of the PK studies submitted, it can be concluded that no dosage adjustments are needed for concomitant administration of either tacrolimus or voriconazole with anidulafungin. Also, the pediatric PK studies indicated that a loading dose of 1.5 mg/kg administered on Day 1 followed by daily administration of 0.75 mg/kg to pediatric patients result in systemic exposures that are comparable to those achieved in adults who receive a 100 mg loading dose followed by daily administration of 50 mg. The applicant is not seeking a pediatric indication in this resubmission and has not included the results from the pediatric studies in the package insert.

No outstanding clinical pharmacology issues were identified with anidulafungin in this current NDA submission.

A. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Clinical Pharmacology 4 has reviewed the clinical pharmacology information included in this resubmission of NDA 21-632 for Anidulafungin and the reviewer has deemed this information to be acceptable. The Human Pharmacokinetics and Bioavailability Section of NDA 21-632 has met the requirements of the 21 CFR.

B. Phase IV Commitments

There are no clinical pharmacology and biopharmaceutics Phase IV commitments.

Dakshina M. Chilukuri, Ph.D. _____
Division of Clinical Pharmacology and Biopharmaceutics 4
Office of Clinical Pharmacology and Biopharmaceutics

Initialed by Philip Colangelo, Pharm D., Ph.D. _____
cc: NDA 21-632 and CDR (Biopharm)

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C. Clinical Pharmacology Summary

Drug-Drug Interaction Studies:

1. The co-administration of VFEND® (voriconazole) and anidulafungin appeared safe and was tolerated with only mild discomfort by the group of healthy male subjects in this study. Co-administration of voriconazole with anidulafungin had no clinically significant differences on the pharmacokinetics of anidulafungin. The 90% CIs of the mean ratios of the test treatment (anidulafungin plus voriconazole) versus reference treatment (anidulafungin alone) were within the 80 - 125% equivalence range. Co-administration of anidulafungin with voriconazole had no clinically significant differences on the pharmacokinetics of voriconazole or its N-oxide metabolite. The 90% CIs of the mean ratios of the test treatment (voriconazole plus anidulafungin) versus reference treatment (voriconazole alone) were within the 80 - 125% equivalence range.
2. Co-administration of tacrolimus with anidulafungin did not result in any clinically significant differences on the pharmacokinetics of anidulafungin. The 90% CIs of the mean ratios of the test treatment (anidulafungin co-administered with tacrolimus) versus reference treatment (anidulafungin alone) were within the 80 - 125% equivalence range. Co-administration of anidulafungin with tacrolimus did not result in any clinically significant differences on the pharmacokinetics of tacrolimus. The 90% CIs of the mean ratios of the test treatment (tacrolimus co-administered with anidulafungin) versus reference treatment (tacrolimus alone) were within the 80 - 125% equivalence range. The co-administration of tacrolimus with anidulafungin appeared to be well tolerated by the group of healthy male subjects in this study. Five of the 36 subjects enrolled in this study experienced adverse events of elevated ALT on Day 12 or 16. The subjects experiencing these events were asymptomatic, and mild transient elevations such as these have been noted in other studies of anidulafungin. It is therefore unlikely that these events are related to coadministration of anidulafungin and tacrolimus.

Pediatric PK study:

Daily infusions of 0.75 mg/kg and 1.5 mg/kg of anidulafungin for at least 5 days were well tolerated by immuno-compromised children from ages 2 to 17 years with neutropenia. Anidulafungin exhibited linear pharmacokinetics when administered at dosages of 0.75 mg/kg/day and 1.5 mg/kg/day to children aged 2 to 17 years with neutropenia. The pharmacokinetic profiles of anidulafungin administered to children on a weight-adjusted basis of 0.75 and 1.5 mg/kg/day were similar to profiles of anidulafungin administered to adults at dosages of 50 and 100 mg/day. No child with neutropenia was diagnosed with an invasive fungal infection during treatment with anidulafungin.

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_____ § 552(b)(4) Draft Labeling

Appendix B. Individual Study Reviews

Report AA03489: Phase 1, Double-Blind, Multiple Dose, Randomized, Crossover, Pharmacokinetic Interaction Study Between VFEND® (Voriconazole) and Anidulafungin

Objectives:

The primary objective of this study was to assess the possible pharmacokinetic interaction of co-administration of VFEND® (voriconazole) and anidulafungin at steady state conditions in healthy male subjects.

The secondary objective of this study was to assess the safety and tolerability of co-administration of VFEND® (voriconazole) and anidulafungin in healthy male subjects.

Subjects: 24 healthy subjects between 18 and 55 years were selected.

Study design:

This study was a double-blind, third party unblinded, randomized, three period, multiple-dose, crossover, pharmacokinetic interaction study. It was conducted over approximately 68 days with a washout period of at least 10 days between dosing within study periods. Subjects received each of the following three treatments in separate dose periods: IV anidulafungin plus voriconazole placebo (Treatment A), anidulafungin placebo plus voriconazole (Treatment B), and IV anidulafungin plus voriconazole (Treatment C).

Subjects received a single 200 mg dose of anidulafungin (or placebo) administered as an intravenous (IV) infusion made to 400 mL with dextrose injection 5%, USP (concentration 0.5 mg/mL) and given over 200 minutes in the morning on Day 1 as a loading dose. Subjects received a single 100 mg dose of anidulafungin (or placebo) administered as an IV infusion made to 200 mL with dextrose injection 5%, USP (concentration 0.5 mg/mL) and given over 100 minutes in the mornings on Days 2 - 4 as the maintenance dose.

Subjects received two initial loading doses of voriconazole 2 x 200 mg tablets (or placebo) every 12 hours on Day 1, followed by maintenance doses of voriconazole 1 x 200 mg tablet or placebo every 12 hours on Days 2 - 3 and the morning of Day 4, administered with 240 mL of ambient temperature water. Dosing with voriconazole active or placebo was to commence each morning 2 hours after the start of the IV infusion of anidulafungin on Days 1 - 4 and at 12 hours after the morning dose on Days 1 - 3. Subjects fasted at least 1 hour before and after each voriconazole and voriconazole placebo dose.

IV infusions of anidulafungin active or placebo were administered in the mornings on Days 1 through 4. Dosing with oral voriconazole active or placebo commenced each morning 2 hours after the start of the IV infusions on Days 1 through 4. A second voriconazole active or placebo dose was given 12 hours after the morning dose on Days 1 through 3. Subjects received only a morning dose on Day 4. Blood samples were collected at specific time points. Anidulafungin plasma concentrations were assayed using a validated LC-MS/MS analytical method, and voriconazole and N-oxide metabolite were analyzed by a validated HPLC method with MS/MS detection.

Criteria for Evaluation:**Pharmacokinetics:**

Plasma Anidulafungin, Voriconazole, and Voriconazole N-oxide Metabolite:

Pharmacokinetic assessments consisted of blood sampling for the analysis of plasma concentrations of anidulafungin, voriconazole, and voriconazole N-oxide metabolite. Blood samples were taken at Hour 0 (predose on Day 1) and 24, 48, 72, 72.5, 73.67, 74.25, 74.5, 75, 75.5, 76, 78, 80, 82, 86, 96, 120, 192, 240, and 312 hours relative to the first dose of anidulafungin or IV placebo on Day 1 of each study period. Blood sampling was designed to adequately evaluate trough concentrations and steady-state concentrations of both drugs. Anidulafungin, voriconazole, and the N-oxide metabolite of voriconazole were assayed in plasma using validated assays.

Safety: Safety laboratory tests, physical examinations, vital signs (blood pressure, pulse, and temperature), electrocardiograms (ECGs), and adverse events (AEs) were evaluated as comparisons for both within and between each treatment group.

Pharmacokinetic Results:

Anidulafungin: Administration of anidulafungin alone (reference) and co-administration of anidulafungin with voriconazole (test) showed similar anidulafungin concentration-time profiles, peak plasma concentrations (C_{max}), as well as similar anidulafungin pharmacokinetic parameters (CL , V_{ss} , and AUC_{ss}). Moreover, the $t_{1/2}$ values of anidulafungin following administration of anidulafungin alone and anidulafungin plus voriconazole were similar. The statistical comparisons of natural log-transformed plasma anidulafungin pharmacokinetic parameters C_{max} and AUC_{ss} between the test and the reference treatments indicated that co-administration of voriconazole had no effect on the pharmacokinetics of anidulafungin. The 90% CI of the mean ratios of the test versus reference treatments were within the 80 - 125% equivalence range. Also, the 90% CI of the mean ratios for natural log-transformed pharmacokinetic parameters CL , V_{ss} , and $t_{1/2}$ for the comparison of test and reference treatments were within the 80 -125% equivalence range.

The arithmetic mean (SD), 90% CI, and % mean ratio of plasma anidulafungin pharmacokinetic parameters following administration of anidulafungin alone (Treatment A, reference) and anidulafungin plus voriconazole (Treatment C, test) are summarized in the following table:

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Summary of the Pharmacokinetic Parameters of Anidulafungin Following Administration of Anidulafungin Plus Voriconazole (Test) Versus Anidulafungin Plus Voriconazole Placebo (Reference)

| Pharmacokinetic Parameters | Steady State Anidulafungin | | | | | |
|--------------------------------|---------------------------------|-------|-----------------|---|---------------|--------------|
| | Anidulafungin Plus Voriconazole | | | Anidulafungin Plus Voriconazole Placebo | | |
| | Arithmetic Mean | SD | Arithmetic Mean | SD | 90% CI * | % Mean Ratio |
| C _{max} (µg/mL) | 7.91 | 1.32 | 7.87 | 1.64 | 96.93-104.35 | 100.57 |
| AUC ₀₋₂₄ (ng*hr/mL) | 117.9 | 21.35 | 120.3 | 24.07 | 94.85- 99.94 | 97.36 |
| T _{max} (hr) | 2.16 | 0.646 | 1.90 | 0.402 | - | - |
| t _{1/2} (hr) | 38.9 | 2.68 | 40.2 | 5.65 | 92.78-103.13 | 97.81 |
| CL (L/hr) | 0.680 | 0.187 | 0.863 | 0.158 | 100.06-105.42 | 102.71 |
| V _{ss} (L) | 41.47 | 8.825 | 40.11 | 9.580 | 99.45-109.76 | 104.48 |

* = The 90% CI and % Mean Ratio are based on log transformed values.
 - = Not Calculated

Voriconazole and Plasma Voriconazole N-oxide Metabolite: Co-administration of voriconazole with anidulafungin (test) and administration of voriconazole alone (reference) resulted in similar voriconazole and voriconazole N-oxide plasma concentrations and pharmacokinetic parameters. The statistical comparisons of the natural log-transformed voriconazole and voriconazole N-oxide pharmacokinetic parameters C_{max} and AUC₀₋₂₄ showed that co-administration of anidulafungin had no effect on voriconazole or voriconazole N-oxide pharmacokinetics. The 90% CI of the mean ratios of the test versus reference treatments were within the 80 - 125% equivalence range.

The arithmetic mean (SD), 90% CI, and % mean ratio of voriconazole and voriconazole N-oxide pharmacokinetic parameters following voriconazole alone (Treatment B, reference) and voriconazole plus anidulafungin (Treatment C, test) are summarized in the following tables:

Summary of the Pharmacokinetic Parameters of Voriconazole Following Administration of Voriconazole Plus Anidulafungin (Test) Versus Voriconazole Plus Anidulafungin Placebo (Reference)

| Pharmacokinetic Parameters | Steady State Voriconazole | | | | | |
|--------------------------------|---------------------------------|---------|-----------------|---|--------------|--------------|
| | Voriconazole Plus Anidulafungin | | | Voriconazole Plus Anidulafungin Placebo | | |
| | Arithmetic Mean | SD | Arithmetic Mean | SD | 90% CI * | % Mean Ratio |
| C _{max} (ng/mL) | 3710 | 1190 | 3960 | 1190 | 89.40- 99.19 | 93.69 |
| AUC ₀₋₂₄ (ng*hr/mL) | 29511.2 | 13372.5 | 29957.6 | 15736.2 | 92.13-103.00 | 97.41 |
| T _{max} (hr) | 1.64 | 0.375 | 1.55 | 0.692 | - | - |

* = The 90% CI and % Mean Ratio are based on log transformed values.
 - = Not Calculated

Summary of the Pharmacokinetic Parameters of Voriconazole N-oxide Metabolite Following Administration of Voriconazole Plus Anidulafungin (Test) Versus Voriconazole Plus Anidulafungin Placebo (Reference)

| Pharmacokinetic Parameters | Steady State Voriconazole N-Oxide Metabolite | | Steady State Voriconazole N-Oxide Metabolite | | 90% CI * | % Mean Ratio |
|--------------------------------|--|---------------------------------|--|---|--------------|--------------|
| | Voriconazole Plus Anidulafungin | Voriconazole Plus Anidulafungin | Voriconazole Plus Anidulafungin Placebo | Voriconazole Plus Anidulafungin Placebo | | |
| | Arithmetic Mean | SD | Arithmetic Mean | SD | | |
| C _{max} (ng/mL) | 3700 | 906 | 3860 | 973 | 87.25-104.91 | 95.67 |
| AUC ₀₋₂₄ (ng*hr/mL) | 39581.0 | 9294.30 | 41930.9 | 10261.3 | 86.99-102.46 | 94.41 |
| T _{1/2} (hr) | 4.97 | 2.61 | 5.78 | 2.89 | - | - |

* = The 90% CI and % Mean Ratio are based on log transformed values.
 - = Not Calculated

Conclusion:

- The co-administration of VFEND® (voriconazole) and anidulafungin appeared safe and was tolerated with only mild discomfort by the group of healthy male subjects in this study.
- Co-administration of voriconazole with anidulafungin had no clinically significant differences on the pharmacokinetics of anidulafungin. The 90% CIs of the mean ratios of the test treatment (anidulafungin plus voriconazole) versus reference treatment (anidulafungin alone) were within the 80 - 125% equivalence range.
- Co-administration of anidulafungin with voriconazole had no clinically significant differences on the pharmacokinetics of voriconazole or its N-oxide metabolite. The 90% CIs of the mean ratios of the test treatment (voriconazole plus anidulafungin) versus reference treatment (voriconazole alone) were within the 80 - 125% equivalence range.
- On the basis of a lack of any pharmacokinetic drug interaction, co-administration of voriconazole and anidulafungin may be a suitable combination for study in future efficacy trials.

Report VER002-15: Phase 1, Open-Label, Single-Sequence, Pharmacokinetic Interaction Study Between Oral Tacrolimus (Prograf, Fujisawa Healthcare, Inc.) and Intravenous Anidulafungin In Healthy Male Subjects

Objectives:

Primary: To assess the possible pharmacokinetic interaction of co-administration of oral tacrolimus (Prograf®) and intravenous anidulafungin in healthy male subjects.

Secondary: To assess the safety and tolerability of co-administration of oral tacrolimus (Prograf®) and intravenous anidulafungin in healthy male subjects.

Study design:

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This study was a single-sequence, open-label, pharmacokinetic interaction study. The study was conducted over approximately 1 month, which included screening through study discharge. Following screening, subjects returned to the Clinical Research Unit (CRU) on the morning of Day -1 for clinical laboratory evaluations. Following laboratory collection, subjects were released and required to return in the evening on Day -1 for clinic confinement. Subjects were screened for drugs of abuse and remained confined until after the pharmacokinetic blood sample was obtained and final discharge procedures were completed on Day 16.

On Days 1 and 13, all subjects were administered a single oral 5 mg dose of tacrolimus with pharmacokinetic blood sampling through 72 hours postdose. On Day 4, a 200 mg loading intravenous (IV) dose of anidulafungin was administered with daily maintenance doses of 100 mg administered on Days 5 through 13. A predose and trough blood sample for anidulafungin was collected on Days 4 and 8, respectively. Serial pharmacokinetic blood samples for the assay of anidulafungin in plasma were collected on Days 10 and 13 through 24 hours postdose.

Criteria for Evaluation:

Pharmacokinetics:

Blood samples were collected at multiple times following administrations of tacrolimus and anidulafungin to assess concentrations of tacrolimus in blood and anidulafungin in plasma. The pharmacokinetics of anidulafungin were determined at steady state when anidulafungin was administered alone (Day 10) and when administered with tacrolimus (Day 13). The pharmacokinetics of tacrolimus were assessed following a single dose administered alone (Day 1) and following multiple doses of anidulafungin (Day 13).

Pharmacokinetic Results:

Administration of anidulafungin alone (reference) and co-administration of anidulafungin with tacrolimus (test) showed similar anidulafungin concentration-time profiles, peak plasma concentrations (C_{max}) and AUC_{ss}. The statistical comparisons of natural log-transformed plasma anidulafungin pharmacokinetic parameters C_{max} and AUC_{ss} between the test and the reference treatments indicated that single dose co-administration of tacrolimus had no effect on the steady state pharmacokinetics of anidulafungin. The 90% CIs of the mean ratios of the test versus reference treatments were within the 80 - 125% equivalence range. The estimates of plasma anidulafungin pharmacokinetic parameters following administration of anidulafungin alone (reference) and anidulafungin co-administered with tacrolimus (test) are summarized in the following table:

Plasma Steady-State Anidulafungin Pharmacokinetic Parameters Following Co-administration of Anidulafungin with Tacrolimus (Test) Versus Anidulafungin Alone (Reference)

| Pharmacokinetic Parameters | Co-administered with | | 90% CI | % Mean Ratio |
|-------------------------------|----------------------|----------------------|---------------|--------------|
| | Tacrolimus* | Anidulafungin Alone* | | |
| C _{max} (mg/L) | 7.07 (22.0) | 6.88 (21.6) | 99.5 - 106.1 | 102.8 |
| AUC ₀₋₂₄ (mg*hr/L) | 110.8 (20.4) | 103.4 (21.6) | 105.1 - 109.4 | 107.2 |
| t _{max} (hr) | 1.71 (1.58, 6.01) | 1.70 (1.64, 8.00) | NC | NC |
| t _{1/2} (hr) | 25.2 (5.9) | 25.2 (7.2) | NC | NC |
| CL (L/hr) | 0.923 (0.21) | 0.993 (0.24) | NC | NC |
| V _d (L) | 32.3 (8.7) | 35.2 (14.4) | NC | NC |

*For C_{max} and AUC₀₋₂₄, the Geometric Mean (%CV) is presented, the arithmetic mean (SD) is presented for other parameters
 Note: For t_{max}, the Median (Minimum and Maximum) are provided.
 NC: Not calculated

Tacrolimus: Co-administration of tacrolimus with anidulafungin (test) and administration of tacrolimus alone (reference) resulted in similar tacrolimus whole blood concentrations and pharmacokinetic parameters. The statistical comparisons of the natural log-transformed tacrolimus pharmacokinetic parameters C_{max} and AUCs showed that co-administration of anidulafungin had no effect on tacrolimus pharmacokinetics. The 90% CIs of the mean ratios of the test versus reference treatments were within the 80 - 125% equivalence range.

- The estimates of whole blood tacrolimus pharmacokinetic parameters following tacrolimus alone (reference) and tacrolimus co-administered with anidulafungin (test) are summarized in the following table:

Whole Blood Tacrolimus Pharmacokinetic Parameters Following Co-administration of Anidulafungin with Tacrolimus (Test) Versus Tacrolimus Alone (Reference)

| Pharmacokinetic Parameters | Co-administered with | | 90% CI | % Mean Ratio |
|---------------------------------|----------------------|-------------------|----------------|--------------|
| | Anidulafungin* | Tacrolimus Alone* | | |
| C _{max} (ng/mL) | 22.5 (33.6) | 23.2 (42.4) | 90.26 - 109.06 | 99.2 |
| C _{12h} (ng/mL) | 4.1 (39.4) | 3.9 (42.0) | 97.48 - 120.97 | 108.6 |
| AUC ₀₋₁₂ (ng*hr/mL) | 102.6 (27.3) | 107.8 (39.8) | 89.04 - 106.16 | 97.2 |
| AUC ₀₋₂₄ (ng*hr/mL) | 228.4 (27.9) | 229.4 (37.0) | 91.75 - 109.83 | 100.4 |
| AUC _{0-inf} (ng*hr/mL) | 270.9 (28.0) | 269.6 (36.9) | 92.77 - 111.22 | 101.6 |
| t _{max} (hr) | 2.00 (1.0, 3.17) | 2.00 (1.0, 3.00) | NC | NC |
| t _{1/2} (hr) | 29.0 (3.2) | 27.8 (3.9) | NC | NC |
| CL/F (L/hr) | 19.4 (6.72) | 20.3 (10.0) | NC | NC |
| V _{Z/F} (L) | 804.3 (263.1) | 823.3 (441.4) | NC | NC |

*For t_{1/2}, CL/F and V_{Z/F} the arithmetic mean (SD) is presented, the geometric mean (%CV) is presented for other parameters
 Note: For t_{max}, the Median (Minimum and Maximum) is presented.
 NC: Not calculated

CONCLUSION:

- Co-administration of tacrolimus with anidulafungin did not result in any clinically significant differences on the pharmacokinetics of anidulafungin. The 90% CIs of the mean ratios of the test treatment (anidulafungin co-administered with tacrolimus) versus reference treatment (anidulafungin alone) were within the 80 - 125% equivalence range.
- Co-administration of anidulafungin with tacrolimus did not result in any clinically significant differences on the pharmacokinetics of tacrolimus. The 90% CIs of the mean ratios of the test treatment (tacrolimus co-administered with anidulafungin)

versus reference treatment (tacrolimus alone) were within the 80 - 125% equivalence range.

- The co-administration of tacrolimus with anidulafungin appeared to be well tolerated by the group of healthy male subjects in this study. Five of the 36 subjects enrolled in this study experienced adverse events of elevated ALT on Day 12 or 16. The subjects experiencing these events were asymptomatic, and mild transient elevations such as these have been noted in other studies of anidulafungin (VER002-5). It is therefore unlikely that these events are related to coadministration of anidulafungin and tacrolimus.

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Report VER002-12: Phase 1/2 Study of the Safety, Tolerance, and Pharmacokinetics of Anidulafungin in Immunocompromised Children with Neutropenia

Objectives:

Primary: to determine the safety, tolerance, and pharmacokinetic profile of IV anidulafungin as early empirical therapy for prevention of fungal infections in immunocompromised children ages 2 to 17 years with neutropenia.

Secondary: to evaluate the frequency of patients who develop documented deeply invasive breakthrough fungal infection.

Study design:

This was a Phase 1/2 multi-center, open-label, sequential dose-escalation study (maintenance doses from 0.75 mg/kg/day to 1.5 mg/kg/day) designed to assess the safety, tolerance, and pharmacokinetics of IV anidulafungin administered as early empirical therapy to 24 immunocompromised children ages 2 to 17 years with neutropenia. Children were stratified by age, from 2 to 11 years and from 12 to 17 years. Dose escalation in each age cohort could proceed independently of the other age cohort following an interim analysis of safety and pharmacokinetic data conducted by the Vicuron Safety Committee, with review and concurrence by the investigators, when all patients within an age cohort completed therapy or received study drug for at least 5 days. The study was conducted at 5 sites in the USA. The PK sampling and analysis was conducted according to traditional method.

Criteria for Evaluation:

Pharmacokinetics:

A total of 320 anidulafungin plasma concentrations were obtained from 24 pediatric patients using traditional PK sampling scheme at various time intervals. Pharmacokinetic analysis was conducted using noncompartmental method. Mean Day 1 anidulafungin plasma concentration-time profiles from patients who received 1.5 mg/kg/day loading dose and mean Day 5 anidulafungin plasma concentration-time profiles from patients in the 1.5 mg/kg/day maintenance dosage group are shown in Figure 1 and Figure 2, respectively. Corresponding profiles for patients who received 3.0 mg/kg loading dose on Day 1 followed by 1.5-mg/kg/day maintenance doses on Days 2-5 are shown in Figure 3 and Figure 4, respectively.

Figure 1: Mean (+/- Standard Deviation) Anidulafungin Plasma Concentration-Time Profiles Following a Loading Dose of 1.5 mg/kg (Dosage Group 1, Day 1)

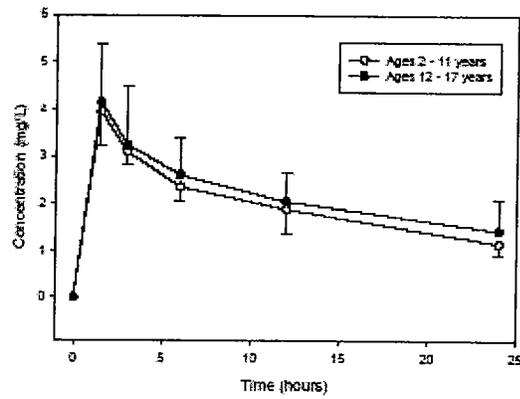


Figure 2: Mean (+/- Standard Deviation) Anidulafungin Steady-State Plasma Concentration-Time Profiles Following Daily Doses of 0.75 mg/kg (Dosage Group 1, Day 5)

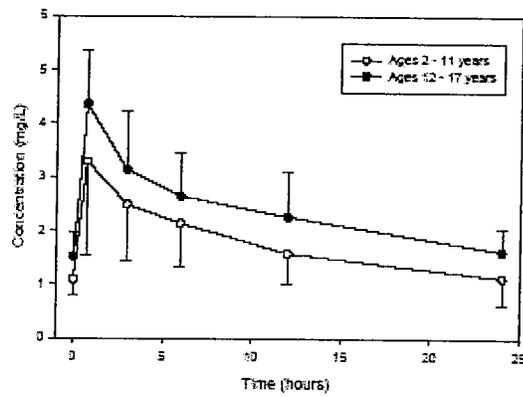


Figure 3: Mean (+/- Standard Deviation) Anidulafungin Plasma Concentration-Time Profiles Following a Loading Dose of 3.0 mg/kg (Dosage Group 2, Day 1)

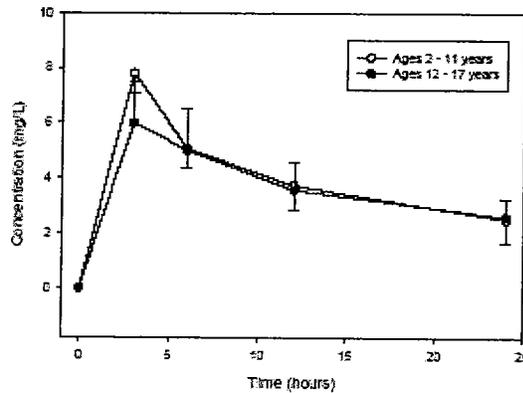
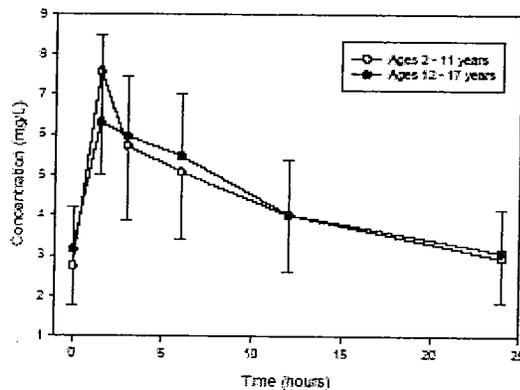


Figure 4: Mean (+/- Standard Deviation) Anidulafungin Steady-State Plasma Concentration-Time Profiles Following Daily Doses of 1.5 mg/kg (Dosage Group 2, Day 5)



Anidulafungin concentration-time profiles were consistent between age cohorts within dosage groups. Between dosage groups, anidulafungin plasma concentration-time profiles were approximately 2-times greater, consistent with the 2-fold higher dosage. A single anomalous profile was observed for Patient 2-02 (in the 2-to-11-year cohort of the 0.75-mg/kg/day maintenance dosage group) on Day 5, whose concentrations were relatively unchanging and below 1 mg/L throughout the dosing interval. The profile observed following the 1.5-mg/kg loading dose, however, was consistent with other patients in the 0.75-mg/kg/day maintenance dosage group. No explanation could be found for this anomaly; patient case report forms showed the patient received the planned dosage and that blood samples were collected as specified in the protocol

Following administration of the 0.75-mg/kg/day maintenance dosage regimen, maximum mean anidulafungin plasma concentrations were approximately 4 mg/L and were maintained above 1 mg/L throughout the dosing interval. Following the 1.5-mg/kg/day maintenance dosage regimen, maximum mean concentrations were approximately 7 mg/L and were maintained above 2 mg/L throughout the dosing interval. Individual trough concentrations through Day 7 are shown in Figure 5 and Figure 6 and show that steady-state concentrations were achieved following the loading dose, and were

maintained at a consistent level throughout treatment. Trough concentrations were also similar across both age cohorts.

Figure 5: Anidulafungin Trough Concentrations For Children Receiving the 0.75-mg/kg/day Dosage Regimen

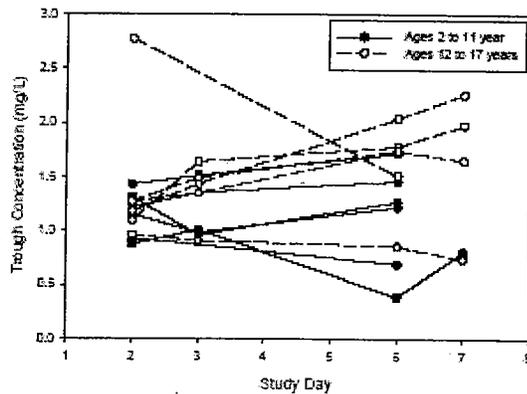
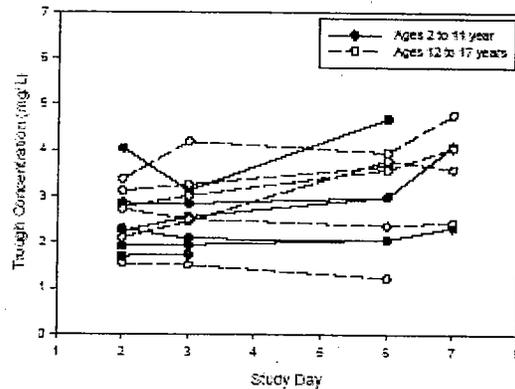


Figure 6: Anidulafungin Trough Concentrations For Children Receiving the 1.5-mg/kg/day Dosage Regimen.



12.2.2

Pharmacokinetic Parameters

Pharmacokinetic parameters are also summarized for Days 1 and 5 in Table 31 and Table 32, respectively. Pharmacokinetic parameters C_{max} and AUC_{0-t} (or AUC_{SS}) were calculated for all patients through the Day 1 and 5 24-hour dosing interval. For Patient 2-09 (Days 1 and 5) and Patient 3-01 (Day 5), there were an insufficient number of samples to determine a terminal slope; no estimates were made for terminal half-life or other terminal slope-dependent parameters.

Table 31: Summary of Anidulafungin Pharmacokinetic Parameters in Children Following a Loading Dose of 1.5 mg/kg or 3.0 mg/kg (Day 1)

| Loading Dose (mg/kg) | Age Cohort (years) | Statistic | C _{max} (mg/L) | AUC ₀₋₂₄ (mg·h/L) | t _{1/2} (h) | CL/Weight (L/hr/kg) | V _{SS} /Weight (L/kg) |
|----------------------|--------------------|-----------|-------------------------|------------------------------|----------------------|---------------------|--------------------------------|
| 1.5 | 2 to 11 | Mean | 3.95 | 46.3 | 17.3 | 0.0208 | 0.468 |
| | | SD | 0.74 | 8.7 | 3.7 | 0.0052 | 0.086 |
| | | CV% | 18.7 | 18.8 | 21.2 | 25.0 | 17.5 |
| | | N | 6 | 6 | 6 | 6 | 6 |
| | 12 to 17 | Mean | 4.10 | 49.6 | 24.3 | 0.0143 | 0.430 |
| | | SD | 1.11 | 14.6 | 8.7 | 0.0062 | 0.133 |
| | | CV% | 27.1 | 29.5 | 35.9 | 43.5 | 31 |
| | | N | 6 | 6 | 6 | 6 | 6 |
| 3.0 | 2 to 11 | Mean | 7.80 | 92.3 | 18.3 | 0.0200 | 0.474 |
| | | SD | 0.76 | 11.9 | 6.7 | 0.0058 | 0.036 |
| | | CV% | 9.7 | 12.8 | 36.7 | 28.7 | 7.6 |
| | | N | 6 | 6 | 6 | 6 | 6 |
| | 12 to 17 | Mean | 5.99 | 87.2 | 20.8 | 0.0181 | 0.523 |
| | | SD | 1.50 | 23.6 | 4.8 | 0.0078 | 0.193 |
| | | CV% | 25.0 | 27.0 | 23.0 | 43.4 | 36.9 |
| | | N | 6 | 6 | 5 | 5 | 5 |

Reference: Table 14.2.6

AUC₀₋₂₄: Area under the plasma concentration-time curve through 24-hour post-dose; CL: Clearance; C_{max}: Maximum plasma concentration; CV%: Coefficient of variation; t_{1/2}: Elimination half-life; SD: Standard deviation; V_{SS}: Volume of distribution at steady state

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Table 32: Summary of Steady-State Anidulafungin Pharmacokinetic Parameters in Children Following Daily Dosages of 0.75 mg/kg or 1.5 mg/kg (Day 5)

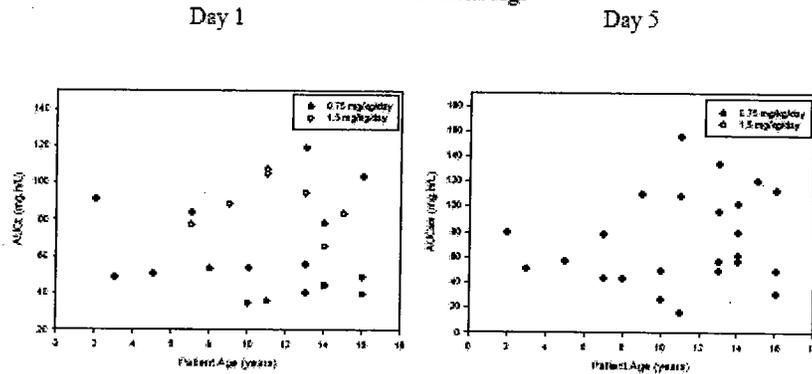
| Dosage (mg/kg/day) | Age Cohort (years) | Statistic | C _{max} (mg/L) | AUC _{SS} (mg-h/L) | t _{1/2} (h) | CL/Weight (L/hr/kg) | V _{SS} /Weight (L/kg) |
|--------------------|--------------------|-----------|-------------------------|----------------------------|----------------------|---------------------|--------------------------------|
| 0.75 | 2 to 11 | Mean | 3.32 | 41.1 | 20.3 | 0.0217 | 0.575 |
| | | SD | 1.66 | 15.8 | 7.9 | 0.0123 | 0.243 |
| | | CV% | 50.1 | 38.5 | 38.7 | 56.7 | 42.3 |
| | | N | 6 | 6 | 6 | 6 | 6 |
| | 12 to 17 | Mean | 4.35 | 56.2 | 26.0 | 0.0133 | 0.499 |
| | | SD | 0.98 | 15.6 | 10.2 | 0.0031 | 0.231 |
| | | CV% | 22.6 | 27.8 | 39.2 | 23.1 | 46.3 |
| | | N | 6 | 6 | 5 | 5 | 5 |
| 1.5 | 2 to 11 | Mean | 7.57 | 96.1 | 18.9 | 0.0163 | 0.419 |
| | | SD | 2.59 | 38.0 | 3.5 | 0.0048 | 0.066 |
| | | CV% | 34.2 | 39.6 | 18.3 | 29.8 | 15.8 |
| | | N | 6 | 6 | 6 | 6 | 6 |
| | 12 to 17 | Mean | 6.88 | 102.9 | 21.1 | 0.0156 | 0.449 |
| | | SD | 1.67 | 29.0 | 5.2 | 0.0079 | 0.166 |
| | | CV% | 24.3 | 28.2 | 24.8 | 50.2 | 37.0 |
| | | N | 6 | 6 | 5 | 6 | 5 |

Reference: Table 14.2.7

AUC_{SS} Area under the plasma concentration-time curve at steady state; CL Clearance; C_{max} Maximum plasma concentration; CV% Coefficient of variation; t_{1/2} Elimination half-life; SD Standard deviation; V_{SS} Volume of distribution at steady state

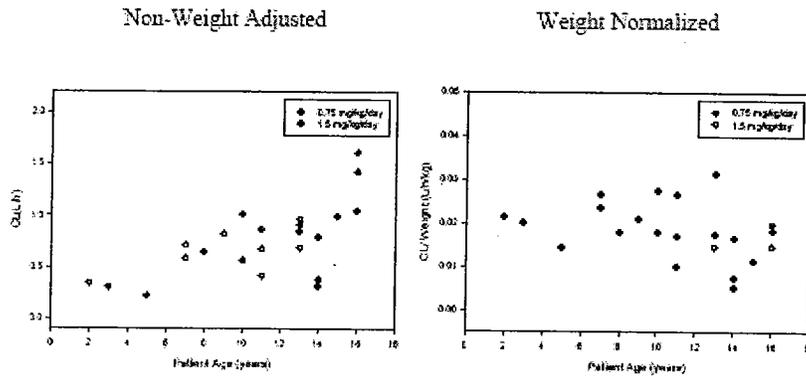
Drug exposure was also similar between age cohorts within dosage groups. Mean AUC_{SS} was 41.1 and 56.2 mg-h/L for younger and older cohorts, respectively, receiving the 0.75-mg/kg/day regimen. Exposures increased in a manner consistent with dose proportionality, and were 96.1 and 102.9 mg-h/L for younger and older children, respectively, receiving the 1.5-mg/kg/day regimen. There was no relationship between drug exposure and patient age (Figure 8). Clearance and V_{SS} were dependent upon age, but when weight-normalized showed no differences between age cohorts or between dosage groups (Figure 9 and Figure 10, respectively). A disposition half-life was estimated within the limitations of sampling and the 24-hour sampling interval employed by the study. The t_{1/2} was approximately 1 day and was not dependent upon age or dosage (Figure 11).

Figure 8: Area Under the Anidulafungin Plasma Concentration-Time Curve Versus Patient Age

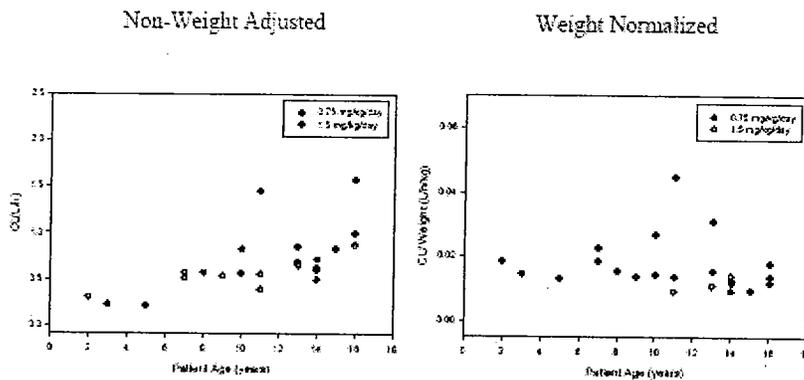


Reference: Table 14.2.4, Table 14.2.5, and Appendix 16.2

Figure 9: Anidulafungin Clearance Versus Patient Age
Day 1



Day 5

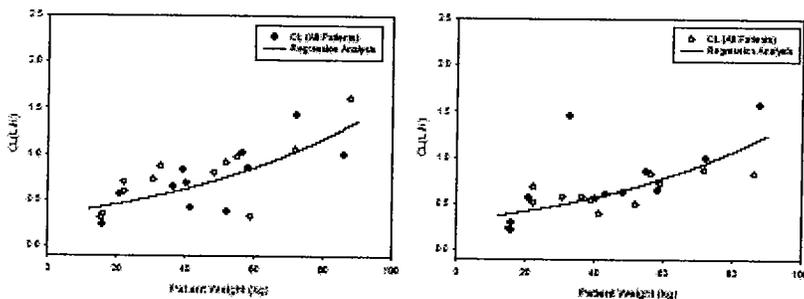


Reference: Table 14.2.4, Table 14.2.5, and Appendix 16.2

There was no relationship between patient age and C_{max} , AUC, weight-normalized CL, or weight-normalized V_{SS} ; the percentage of variance explained by patient age and body weight did not exceed 12%. Clearance and V_{SS} were dependent upon patient age and body weight; dependence of CL and V_{SS} on patient age is explained by the interdependence of age and body weight. Weight-normalized CL and V_{SS} were not

dependent upon age. Plots of CL and V_{SS} versus patient weight are presented in Figure 12 and Figure 13, respectively.

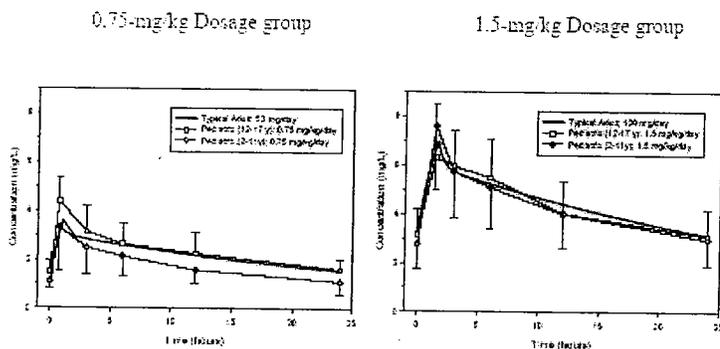
Figure 12: Anidulafungin Clearance Versus Body Weight
Day 1 Day 5



Reference: Appendix 16.1.13

Pediatric maintenance dosages used in this study (0.75 and 1.5 mg/kg/day) were chosen to match anidulafungin concentrations and exposures achieved with maintenance dosages used in adult clinical studies (50 and 100 mg/day). As anidulafungin is degraded in the body and not metabolized or processed by the kidneys, dosages were extrapolated based on patient weight. Anidulafungin concentration-time profiles in pediatric patients receiving 0.75 or 1.5 mg/kg/day were similar to adults receiving 50 or 100 mg/day, respectively. A plot of steady-state anidulafungin concentrations versus time in pediatric patients (Day 5) are compared to a typical adult patient with esophageal candidiasis in Figure 14. The concentrations for the adult patient receiving 50 mg/day and 100 mg/day, respectively, were determined from an adult population pharmacokinetic model.

Figure 14: Comparison of Steady-State Anidulafungin Concentrations Between Pediatric Patients (Day 5) and a Typical Adult With Esophageal Candidiasis



Reference: Table 14.2.3, Dowell 2004, and Victor Report RAVES00100 2003.
Error bars are standard deviations.

Three hundred twenty anidulafungin plasma concentrations were obtained from 24 patients. Anidulafungin plasma concentration-time profiles were approximately 2-fold greater in patients who received 1.5 mg/kg/day of anidulafungin than in patients who received 0.75 mg/kg/day. Anidulafungin plasma concentration-time profiles were similar between age cohorts in each dosage group. Exposure to anidulafungin was age-invariant. There was no relationship between patient age and C_{max} , AUC, weight-normalized CL, or weight-normalized V_{ss} . The pharmacokinetic profiles of anidulafungin administered to children on a weight-adjusted basis of 0.75 and 1.5 mg/kg/day were similar to profiles of anidulafungin administered to adults at dosages of 50 and 100 mg/day. When normalized for weight, anidulafungin displayed linear dose-dependent pharmacokinetics in children 2 to 17 years.

CONCLUSIONS

1. Daily maintenance dose infusions of 0.75 mg/kg and 1.5 mg/kg of anidulafungin for at least 5 days were well tolerated by immuno-compromised children from ages 2 to 17 years with neutropenia.
2. Anidulafungin exhibited linear pharmacokinetics when administered at maintenance dosages of 0.75 mg/kg/day and 1.5 mg/kg/day to children aged 2 to 17 years with neutropenia. The pharmacokinetic profiles of anidulafungin administered to children on a weight-adjusted basis of 0.75 and 1.5 mg/kg/day were similar to the PK profiles of anidulafungin administered to adults at maintenance dosages of 50 and 100 mg/day, respectively.
3. No child with neutropenia was diagnosed with an invasive fungal infection during treatment with anidulafungin.

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/s/

Dakshina Chilukuri
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I've revised the document per your (Renata's) edits

Phil Colangelo
11/18/2005 02:33:38 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics Review

| | |
|---------------------------------|---|
| NDA | 21-632 |
| Drug Product; Brand® | Anidulafungin for injection, 50 mg; N/A |
| Submission Date | April 25, 2003 |
| Applicant | Vicuron Pharmaceuticals Inc. |
| Clinical Division | DSPIDP (HFD-590) |
| OCPB Division | DPE3 (HFD-880) |
| Type of Submission | NDA original submission |
| Reviewer | Dakshina Chilukuri, Ph.D. |
| Pharmacometrics Reviewer | Yaning Wang, Ph.D. |
| Team Leader | Philip Colangelo, Pharm D, Ph.D. |
| Review Date | May 07, 2004 |

I. Executive Summary

The applicant is seeking approval of Anidulafungin, a novel antifungal agent belonging to the Echinocandin class for intravenous (IV) administration in NDA 21-632. The proposed indication is treatment of esophageal candidiasis. The proposed dosage regimen is a loading dose of 100 mg on the first day, followed by a maintenance dose of 50 mg IV once daily for 14-21 days of treatment.

Anidulafungin (1-[(4R,5R)-4,5-dihydroxy-N(2)-[[4''-(pentyloxy)[1,1':4',1''-terphenyl]-4-yl]carbonyl]-L-ornithine]echinocandin B) is a semi-synthetic derivative of a natural product belonging to the echinocandin class of antifungal agents. These compounds are non-competitive inhibitors of (1,3)- β -D-glucan synthase, an enzyme complex involved in the synthesis of glucan, which is the major component of the cell wall of many fungi. It is generally thought that echinocandin antifungal activity requires the rigid cyclopeptide structure to position key fatty acid and amino acid fragments into proper alignment for biological activity.

The Pharmacokinetics (PK) of anidulafungin were determined from a total of 20 clinical studies. Anidulafungin has been studied in healthy subjects in 12 studies of single/multiple doses of IV (9 studies) and oral (3 studies) administration. A mass balance study was also conducted in which 9 subjects received radiolabeled drug (^{14}C -anidulafungin). PK data were obtained from 172 (IV drug) and 52 (oral drug) subjects without fungal infections including subjects with HIV, hepatic impairment, renal impairment, or given concomitant cyclosporine. The PK of IV anidulafungin has also been studied in 259 patients with fungal infections in 6 clinical studies (VER002-4, VER002-6, VER002-7, VER002-11, XBAF, and XBAG); data from 4 of these studies were combined for a population PK analysis (n = 225).

The pharmacokinetics of anidulafungin are characterized by a distribution half-life (0.5-1 hour) and a volume of distribution of 30 – 50 L. Plasma concentrations and exposures of anidulafungin are dose-proportional and have an intersubject variability (coefficient of variation <30%). Using a loading dose on day 1 that is twice the daily maintenance dose, steady state concentrations are achieved following the administration of the second dose. The steady state concentrations (C_{ss}) and exposure (AUC_{ss}) ranged between 3 - 4 mg/L and 50 - 60 mg-h/L, respectively. Anidulafungin has a half-life of approximately 26-40 hours and is 84% protein bound in humans.

The applicant conducted 1 pivotal clinical efficacy study to demonstrate the non-inferiority of anidulafungin in the treatment of esophageal candidiasis compared to the standard of care treatment, 100 mg orally administered fluconazole. The results of the efficacy study suggested that at the end of treatment (14-21 days), anidulafungin was found to be as effective as fluconazole in the treatment of esophageal candidiasis. However, at follow-up, that is, 14 days after end of treatment, there were a statistically significant higher number of relapses of fungal infections for the group of patients who were treated with IV anidulafungin compared with oral fluconazole. Thus, anidulafungin was found to be effective in the treatment of esophageal candidiasis at the end of treatment but was found to be ineffective in complete resolution of the disease.

The pivotal Phase III clinical study VER002-4 was a randomized, double-blind, double-dummy study of IV anidulafungin versus oral fluconazole in the treatment of esophageal candidiasis. Following study completion, but prior to unblinding of study results, anidulafungin assays of plasma samples from a subset of anidulafungin-randomized patients revealed that approximately 75% of samples did not have quantifiable levels of anidulafungin. A subsequent investigation determined that a systematic error occurred at the contractor responsible for the patient medication kits. This error resulted in a 1:1 reversal of active drug:placebo for 70% of patients. The investigation also confirmed that medication kits were properly assembled with no kit containing both drugs or both placebos.

The sponsor notified the FDA regarding this error prior to unblinding, and an agreed action plan was implemented. The bioanalytical data, generated as part of the action plan and further investigational assays, were consistent with the corrected patient treatment assignment table. All samples taken from patients assigned to a particular drug contained that drug. However, some unexpected drug concentrations were found in a few samples. The majority of samples with unexpected bioanalytical data were generated at one site (Site # 19), and unrelated to the error in medication kit selection and distribution. A commissioned audit of this site failed to reveal definitive sources of error.

An inspection of Site # 19 by the Department of Scientific Investigations (DSI) confirmed that a systematic error was indeed made in switching of the treatments. Based on DSI's recommendations, the review division asked the applicant to re-analyze all available plasma samples for both anidulafungin and fluconazole. Following completion of the re-analysis of the plasma samples, no additional problems were identified at the site.

Efficacy and safety analyses conducted by FDA statistician excluding Site # 19 indicated that the results and conclusions were unaffected. Errors unrelated to kit selection, largely limited to a subset of patients at one site, resulted in unexpected bioanalytical findings that likewise did not affect the integrity of the study. The above-mentioned errors are not likely to impact the results of the population PK analysis.

No outstanding clinical pharmacology issues were identified with anidulafungin in this current NDA submission.

Upon review of the efficacy and safety data, the clinical division recommends that anidulafungin is approvable. Based on the action, the revisions and comments to the proposed labeling for the product will be addressed at a later date.

A. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III has reviewed the information included in original NDA 21-632 for Anidulafungin and the reviewer has deemed this information to be acceptable. The Human Pharmacokinetics and Bioavailability Section of NDA 21-632 has met the requirements of the 21 CFR.

B. Phase IV Commitments

There are no clinical pharmacology and biopharmaceutics Phase IV commitments.

Dakshina Chilukuri, Ph.D.

Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Initialed by Philip Colangelo, Pharm D, Ph.D.

cc: NDA 21-632, HFD-590, HFD-880 and CDR (Biopharm)

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II. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics in healthy subjects

Anidulafungin has been studied in healthy subjects without fungal infections in 12 studies of single/multiple doses following IV (9 studies) and oral (3 studies) administration. One of these 12 studies was a mass balance study in which 9 subjects received radiolabeled drug (¹⁴C- anidulafungin). PK data were obtained from 172 (IV drug) and 52 (oral drug) subjects without fungal infections including subjects with HIV, hepatic impairment, renal impairment, or given concomitant cyclosporine.

Pharmacokinetics in patients

The PK of IV anidulafungin has been studied in 259 patients with fungal infections in 6 clinical studies (VER002-4, VER002-6, VER002-7, VER002-11, XBAF, and XBAG); data from 4 of these studies were combined for a population PK analysis (n = 225). The PK of oral anidulafungin has been studied in 72 patients with fungal infections in 2 clinical studies; population PK analyses were performed for both of these studies of oral anidulafungin.

Distribution

IV anidulafungin has been studied in healthy subjects enrolled in single- and multiple-dose studies. Single dose administrations ranged from 7 to 100 mg and were given to 43 healthy subjects included in PK analyses in Clinical Studies XBAE and 101L. Multiple-dose regimens ranged from a total of 120 mg in a 7-day regimen to 1430 mg in a 10-day regimen; 52 healthy subjects were included in the PK analyses of these dose-escalation studies (XBAU, VER002-1 and VER002-5). PK after single or multiple doses were similar and gender-independent. In multiple-dose studies, steady state was achieved following the second dose when a 2:1 LD:MD ratio was used. Plasma drug concentrations and exposures were dose-proportional. Intersubject variability (%CV) for drug concentrations and AUC was generally $\leq 30\%$. C_{max} was reached at or shortly after the end of infusion. V_{ss} was consistent (roughly 30 to 50 L) across all tested doses and approximated total body water volume, suggesting that the drug is well distributed. Also, CL and $t_{1/2}$ were consistent across all studied doses at approximately 1 L/h and 26-40 hours, respectively.

The PK parameters of anidulafungin following multiple daily IV administrations in XBAU, VER002-1, and VER002-5 were generally consistent with those observed in the single-dose studies. C_{max} was reached at or shortly after the end of infusion. Both C_{max} and AUC_{ss} increased proportionally with dose. The PK parameters V_{ss} , CL, and $t_{1/2}$ were in the range of those seen in single-dose studies. Although $t_{1/2}$ varied from study to study (possibly influenced by the times and duration of sampling), it was found to be dose-independent within each individual study.

The PK parameters of IV anidulafungin were derived from a population PK analysis of patients in 4 recently completed and ongoing clinical studies (VER002-4, VER002-6, VER002-7, and VER002-11). The complete pharmacometrics review, performed by Yaning Wang, Ph.D., is included in Appendix C. In the patient population model, the median CL, central volume of distribution (V_1), and V_{ss} were estimated to be 0.946 L/h, 9.97 L, and 33.2 L, respectively. The compartmental PK analysis of study XBAE

estimated CL to be ~ 0.013 L/h/kg (0.9 L/h for a 70-kg person) and V_{ss} to be ~ 0.5 L/kg (35 L for a 70-kg person). The CL rate determined in the Phase 1 multiple dose studies of healthy subjects ranged from 0.78 to 1.3 L/h. The V_{ss} in these Phase 1 multiple dose studies were generally in the range of 38 to 48 L.

Metabolism

Anidulafungin is not metabolized by and is not a clinically relevant inhibitor or inducer of cytochrome P450 enzymes. Anidulafungin is eliminated by chemical degradation. Parent drug degrades to a ring-opened product that is further degraded. Evaluation of human feces indicates that some intact drug (approximately 10% of the administered dose) and a ring-opened product, but predominantly a large amount of small tertiary degradants, are excreted following a dose of anidulafungin. The ring-opened product does not have antifungal activity.

Excretion

Based on the results of the mass balance study, approximately 10% of the administered dose were excreted in feces and none of the administered dose was excreted in urine. Overall 30% of the administered dose was recovered from as total radioactivity through 216 h (9 days). Additional samples were taken at a final visit approximately 6 to 8 weeks after the dose. Final samples, collected 6 to 8 weeks after the dose, had negligible or only slightly measurable amounts of radioactivity.

Pharmacokinetics in Special Populations

Renal impairment

PK of anidulafungin were examined in 24 subjects with mild, moderate and severe renal impairment or end-stage renal disease in an open-label study (VER002-3). Renal impairment was defined by estimated creatinine clearance: mild = 51-79 mL/min, moderate = 31-50 mL/min, and severe \leq 30 mL/min. End-stage renal disease subjects were dependent on dialysis. Subjects were given a single 50 mg IV dose of anidulafungin, and plasma samples were collected for 6 days after dosing.

The results of the renal impairment study indicated that there were no changes in anidulafungin PK due to renal impairment. Also, anidulafungin PK parameters were not affected by whether the drug was given before or after dialysis, nor was anidulafungin found in any dialysate samples. The drug was also well tolerated. These results are consistent with nonclinical and clinical data that show the drug is not renally excreted into the urine.

Hepatic impairment

PK of anidulafungin were examined in healthy subjects and those with mild, moderate, or severe hepatic impairment [Child-Pugh scores 5 to 6 (mild), 7 to 9 (moderate), and 10 to 15 (severe)] in an open-label study (VER002-2). Subjects were given a single 50 mg IV dose of anidulafungin, and plasma samples were collected for 6 days after dosing. PK data for 6 healthy subjects and 18 subjects with varying degrees of hepatic impairment were obtained. Anidulafungin concentrations were not increased because of hepatic impairment. C_{max} , AUC, V_{ss} , and CL were similar for healthy subjects, subjects with mild, moderate and severe hepatic impairment.

Drug-Drug Interactions

Based on the *in vitro* results, anidulafungin is unlikely to inhibit or induce the metabolism of drugs dependent on cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. Also, anidulafungin is not a substrate of cytochrome P450 isoforms. Thus, no *in vivo* drug-interaction studies were conducted.

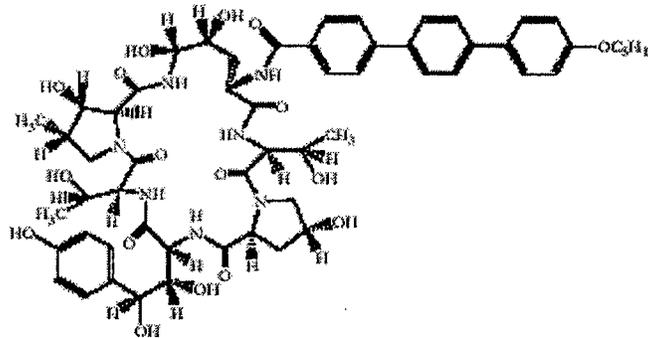
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III. Question Based Review

A. General Attributes

1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?

Anidulafungin (VER002, formerly known as LY303366) is an investigational new drug for intravenous treatment of mucosal and invasive fungal infections. Anidulafungin (1-[(4R,5R)-4,5-Dihydroxy-N(2)-[[4''-(pentyloxy)[1,1':4',1''-terphenyl]-4-yl]carbonyl]-Lornithine] echinocandin B) is a semi-synthetic derivative of a class of antifungal agents called echinocandins. The empirical formula of anidulafungin is $C_{58}H_{73}N_7O_{17}$ and the molecular weight is 1140.3. The structural formula is as shown in Figure 1 below (3.2.S.1.1, 3.2.S.1.2 and 3.2.S.1.3):



The drug product is a lyophilized powder which is manufactured using a standard manufacturing process for sterile products. In addition to the active ingredient, the drug product contains the inactive ingredients fructose, mannitol, polysorbate 80, tartaric acid, and sodium hydroxide and/or hydrochloric acid. These inactive ingredients are widely used in commercial parenteral products. All excipients used for the lyophilized drug product and diluent are compendial (USP/NF) ingredients.

The composition of the commercial formulation is as follows:

Table 1. Composition of Lyophilized Product

| Ingredient | Quantity per vial ^a | Function | Reference to standards |
|--|--------------------------------|-------------------|------------------------|
| Anidulafungin | 50 mg ^a | Active Ingredient | |
| Fructose | 50 mg | | USP |
| Mannitol | 250 mg | | USP |
| Polysorbate 80 | 125 mg | | NF |
| Tartaric Acid | 5.6 mg | | NF |
| | | | USP |
| Sodium hydroxide (NF) and/or hydrochloric acid (NF) solution may be used to adjust pH. | | | |

J

2. What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data (e.g., if disparate efficacy measurements or adverse event reports can be attributed to intrinsic or extrinsic factors that alter drug exposure/response relationships in patients)?

Anidulafungin was evaluated for efficacy in the treatment of esophageal candidiasis in one pivotal phase 3 clinical trial (VER002-4). In the pivotal, Phase 3, randomized, controlled, double-blind, double-dummy study, 601 patients were randomized to IV anidulafungin 100 mg loading dose/50 mg maintenance dose, or oral fluconazole 200 mg loading dose followed by 100 mg maintenance dose (the current standard of care) for 14-21 days. In this population, the primary analysis of efficacy demonstrated that anidulafungin is at least as efficacious as fluconazole, as assessed by endoscopic success at the end of therapy (97.2% in the anidulafungin group; 98.8% in the fluconazole group; treatment difference -1.6%; 95% CI -4.1%, 0.8%).

Table 1: Endoscopic Success in the Clinically Evaluable Population

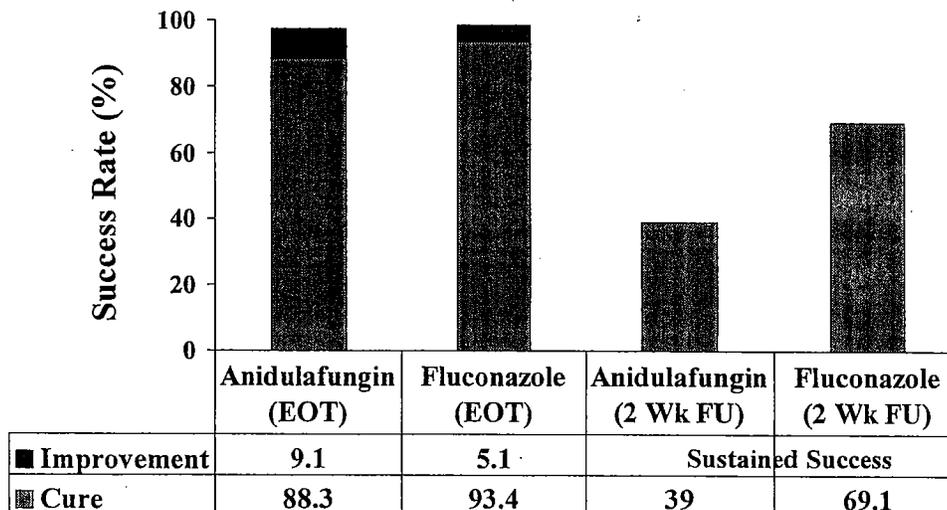
| | Anidulafungin N=249 | Fluconazole N=255 | % Difference* (95% CI) |
|-----------------------|------------------------|----------------------|------------------------------|
| End of Therapy | 242 (97.2%) | 252 (98.8%) | -1.6 (-4.1, 0.8) |

*Calculated as anidulafungin minus fluconazole

The analysis of secondary endpoints at end of therapy, including clinical and mycological responses, and secondary populations, provided confirmation of the primary endpoint. However, clinical and endoscopic relapses occurred at follow-up visits in both anidulafungin and fluconazole treatment groups, supporting the need for chronic suppressive therapy following treatment for esophageal candidiasis. As seen in the figure given below anidulafungin was clearly non-inferior to fluconazole in the treatment of

esophageal candidiasis at the end of treatment, but was inferior to fluconazole at follow-up investigation.

**Phase 3 EC Study: Endoscopy Outcomes
(FDA Analysis: Dr. Imo Ibia)**



These data confirmed and improved upon the proof of concept efficacy data obtained in Phase 2 study XBAF, in which a dose response was observed with endoscopic success rates of 78.6% and 88.9% in patients who received loading/maintenance dose regimen of 50/25 mg and 70/35 mg anidulafungin, respectively.

B. General Clinical Pharmacology

1. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Not Applicable

2. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (if yes, refer to IV. F, Analytical Section; if no, describe the reasons)

Yes, please refer to IV. F, Analytical Section.

3. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

Although the applicant conducted no formal exposure-response analysis, a retrospective analysis of the PK/PD relationship was conducted using data from both oral and IV formulations following completion of the pivotal clinical trials. The highlights of the analysis are summarized below:

- A sigmoidal maximum effect (E_{max}) model was used to describe the PK/PD relationship. Clinical response is associated with drug exposures of greater than 35

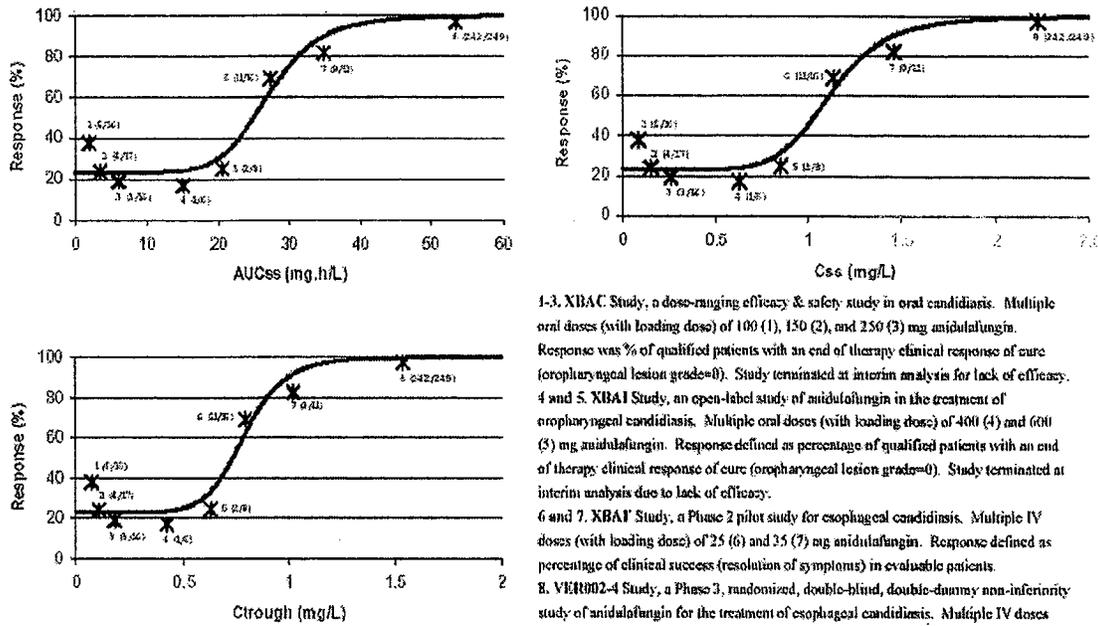
mg·h/L within each dosing interval, average steady state concentrations of 1.5 mg/L, and trough concentrations of greater than 1 mg/L.

- With a 100/50 mg dosage of anidulafungin, steady state is achieved by the second dose and plasma concentrations reach a maximum of approximately 3 to 4 mg/L. Concentrations are maintained above 1 mg/L throughout the dosing period and above 2 mg/L for more than 50% of the dosing period.
- The anidulafungin $t_{1/2}$ is approximately 26-40 hours.
- Clinical trial experience has shown that the concentrations achieved by the 100/50 mg regimen are appropriate for the treatment of esophageal candidiasis.
- In Clinical Study VER002-4, 300 patients were treated with IV anidulafungin (100/50 mg regimen) and 301 patients were treated with oral fluconazole. Duration of treatment for both treatment groups was 14 to 21 days. The primary efficacy endpoint, endoscopic response at the end of therapy, clearly demonstrated the non-inferiority of anidulafungin compared to fluconazole, the current standard of care. At the end of therapy, 242 (97.2%) of 249 clinically evaluable patients in the anidulafungin group had endoscopic success, compared with 252 (98.8%) of the 255 clinically evaluable patients in the fluconazole group.
- Dosage rationale is also based on safety findings of anidulafungin. No protocol-defined MTD was identified in Phase 1 clinical trials in which the highest tested dose of anidulafungin was a 260/130 mg regimen (Clinical Study VER002-5). The proposed 100/50 mg regimen is less than half of the highest anidulafungin dose tested in humans.

A review of the limited information provided by the applicant indicated that the exposure response analysis is incomplete. There appears to be a trend in the PK/PD relationship of anidulafungin (see Figure 6.4 below). Some efficacy was observed following administration of 35 and 25 mg anidulafungin (given with loading doses of 70 and 50 mg, respectively). The AUC corresponding to these dose levels are in the range of 30-37 mg·hr/L and the steady-state concentrations (C_{ss}) are in the range of 1.2-1.5 mg/L. At a higher dose of 50 mg anidulafungin (given with a loading dose of 100 mg), higher efficacy was observed and the corresponding AUC and C_{ss} values are 55 mg·hr/L and 2.3 mg/L. While the analysis provides an indication of the exposure levels needed to achieve efficacy, there is no systematic evaluation of the relationship of exposure and safety of anidulafungin at various doses.

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FIGURE 6.4A. RELATIONSHIP BETWEEN ANIDULAFUNGIN PHARMACOKINETIC PARAMETERS AND CLINICAL EFFICACY IN OROPHARYNGEAL AND ESOPHAGEAL CANDIDIASIS STUDIES.*



* Clinical Response by Study: (n/N) = # responders / # evaluable patients.

1-3. XBAC Study, a dose-ranging efficacy & safety study in oral candidiasis. Multiple oral doses (with loading dose) of 100 (1), 150 (2), and 250 (3) mg anidulafungin. Response was % of qualified patients with an end of therapy clinical response of cure (oropharyngeal lesion grades=0). Study terminated at interim analysis for lack of efficacy.

4 and 5. XBAI Study, an open-label study of anidulafungin in the treatment of oropharyngeal candidiasis. Multiple oral doses (with loading dose) of 400 (4) and 600 (5) mg anidulafungin. Response defined as percentage of qualified patients with an end of therapy clinical response of cure (oropharyngeal lesion grade=0). Study terminated at interim analysis due to lack of efficacy.

6 and 7. XBAF Study, a Phase 2 pilot study for esophageal candidiasis. Multiple IV doses (with loading dose) of 25 (6) and 35 (7) mg anidulafungin. Response defined as percentage of clinical success (resolution of symptoms) in evaluable patients.

8. VER002-4 Study, a Phase 3, randomized, double-blind, double-dummy non-inferiority study of anidulafungin for the treatment of esophageal candidiasis. Multiple IV doses (with loading dose) of 50 mg anidulafungin. Response defined as percentage of patients with an endoscopic response at the end of therapy in the clinically evaluable at end of therapy population.

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a) based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Both C_{max} and AUC were dose-proportional over the range of 6 – 100 mg given as a single dose. As shown in the table and figure below, the clearance and volume of distribution did not change with increasing dose.

TABLE 6.3.2A. MEAN (%CV) PHARMACOKINETIC RESULTS FROM SINGLE-DOSE STUDIES XBAE AND 101L

| Pharmacokinetic Parameters | Doses (mg/kg) in Study XBAE | | | | Doses (mg) in Study XBAE | | | Doses (mg) in Study 101L | | |
|----------------------------|-----------------------------|-----------------------------|-----------------------------|---------------------------|--------------------------|---------------|----------------|--------------------------|---------------|----------------|
| | 0.1 ^a (n = 8) | 0.2 ^a (n = 8) | 0.5 ^a (n = 7) | 1 ^a (n = 4) | 50 (n = 7) | 70 (n = 7) | 100 (n = 7) | 50 (n = 6) | 70 (n = 6) | 100 (n = 6) |
| C_{max} (mg/L) | 0.38 (11.0) | 0.76 (18.9) | 1.72 (18.4) | 3.69 (26.6) | 2.52 (14.9) | 2.91 (23.7) | 3.83 (15.0) | 2.5 (8.4) | 3.35 (15.5) | 4.61 (12) |
| AUC (mg·h/L) | 7.91 (7.4) | 14.4 (14.3) | 37.5 (8.0) | 69.6 (13.5) | 53.3 (14.7) | 69.4 (18.9) | 105 (15.6) | 56.6 (7.0) | 77.5 (13.3) | 116 (13.4) |
| CL (L/h) | 0.91 (10.0) | 1.06 (24.1) | 0.97 (8.9) | 1.11 (26.9) | 0.96 (14.4) | 1.04 (19) | 0.98 (16.2) | 0.89 (6.6) | 0.92 (12.5) | 0.88 (14.1) |
| V_d (L) | 36 (16.3) | 37.6 (21.7) | 44.8 (13.0) | 44.8 (30.5) | 39.4 (16.0) | 44 (23.7) | 38.6 (13.3) | 36.6 (7.1) | 36.7 (15.4) | 33.8 (12.0) |
| $t_{1/2}$ (h) | 31.8 (12.2) | 28 (14.5) | 42 (6.6) | 30.4 (6.8) | 39.3 (8.5) | 45.6 (10.3) | 42.3 (14.8) | 33.2 (11.8) | 36 (10.1) | 33.2 (10.6) |

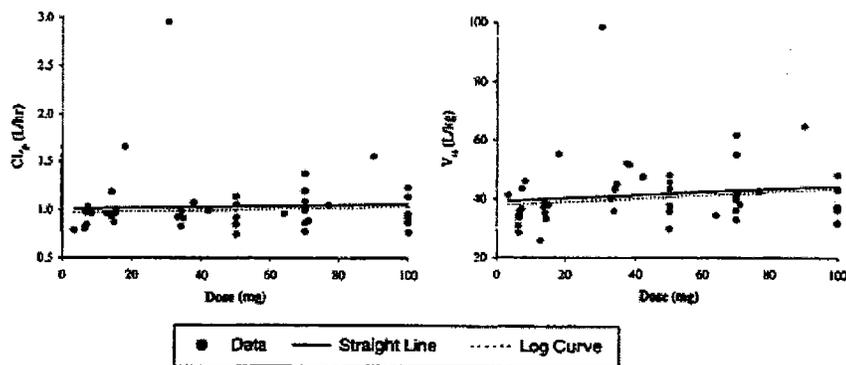


Figure XBAE 5.7.4. Individual LY303366 Clearance (CL_r) and Steady-state Volume of Distribution (V_{ss}) Over the studied dosage range of LY303366.

b) do PK parameters change with time following chronic dosing?

The half-life of anidulafungin obtained from administration of single doses was about 26-40 hours. Following repeat administration, the accumulation ratio was approximately 2. The clearance (CL) and volume of distribution (V_{ss}) at steady state did not change with chronic dosing.

TABLE 6.3.2C. MEAN (%CV) PHARMACOKINETIC RESULTS FROM MULTIPLE-DOSES OF IV ANIDULAFUNGIN IN HEALTHY SUBJECTS

| Study Number | XBAU | XBAU | VER002-1 | VER002-1 | VER002-5 | VER002-5 | VER002-5 |
|------------------------------|-----------------------|-------------|-----------------------|-----------------------|-------------------------|--------------------------|--------------------------|
| Loading Dose (mg/Day 1) | 30 | 70 | 100 | 140 | 150 | 200 | 260 |
| Daily Dose (mg/day) | 15 | 35 | 70 | 100 | 75 | 100 | 130 |
| Number of Patients | (n = 5 ^a) | (n = 6) | (n = 5 ^a) | (n = 3 ^b) | (n = 9 ^c) | (n = 10) | (n = 10) |
| Study Day | 7 | 7 | 10 | 10 | 10 | 10 | 10 |
| C_{24} (mg/L), maximum | 1.60 (23.2) | 3.55 (13.2) | 3.83 (13.4) | 7.17 (3.3) | 4.9 (20.3) | 8.6 (16.2) | 10.9 (11.7) |
| C_{24} (mg/L), average | 0.68 (17.8) | 1.76 (14.5) | 2.36 (11.6) | 4.13 (6.5) | 2.72 ^d (8.8) | 4.66 ^d (24.9) | 7.04 ^d (10.8) |
| AUC ₀₋₂₄ (mg·h/L) | 16.4 (17.8) | 42.3 (14.5) | 56.6 (11.6) | 99.0 (6.5) | 65.5 (8.8) | 111.8 (24.9) | 168.9 (10.8) |
| $t_{1/2}$ (h) | 42.2 (12.5) | 43.2 (17.7) | 26.6 (19.7) | 24.9 (20.1) | 51.2 (6.9) | 52.0 (11.7) | 50.3 (9.7) |
| CL (L/h) | 0.94 (16.2) | 0.84 (13.5) | 1.3 (13.2) | 1.0 (6.7) | 1.15 (8.5) | 0.94 (24) | 0.78 (11.3) |
| V_{ss} (L) | 45 (13.1) | 42.1 (12.9) | 48 (14.6) | 38 (14.5) | 64.8 (18.3) | 47.4 (27.6) | 42.4 (10.4) |

c) how long is the time to the onset and offset of the pharmacological response or clinical endpoint?

Not Applicable

d) are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

In the pivotal efficacy study, a higher relapse rate of esophageal candidiasis was observed in patients treated with IV anidulafungin (100 mg loading dose followed by 50 mg maintenance dose) at follow-up, 14 days after the end of treatment, compared to patients treated with oral fluconazole. This higher relapse rate contrasts with the comparable efficacy seen in the patients in both treatment groups at the end of treatment (14 days). The reasons for this higher relapse rate are not clear. However, this indicates that the dosage regimen used for anidulafungin may not be appropriate for the treatment of esophageal candidiasis. A higher dose or the current dose administered for a longer

duration of time may be more appropriate for anidulafungin for the treatment of esophageal candidiasis.

A retrospective analysis of the effect of exposure (AUC and C_{trough}) of anidulafungin on the relapse rate of patients in the pivotal efficacy study was performed by Dr. Yaning Wang, the pharmacometrics reviewer. However, no statistically significant relationship was found between AUC or C_{trough} and the relapse rate at follow-up for patients in anidulafungin group.

4. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The plasma drug concentration measurements were found to be similar between healthy subjects and patients. Please see below for a comparison of the PK parameters between healthy subjects and patients.

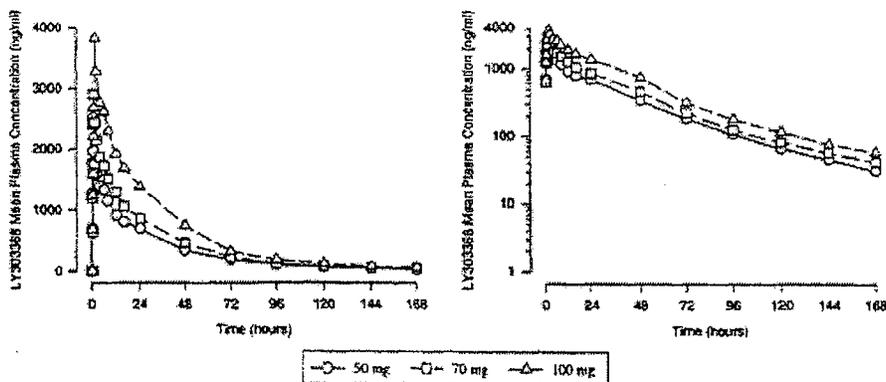
a) what are the basic PK parameters?

The mean (CV as %) PK parameters in healthy volunteers following single dose administration are given below:

| Pharmacokinetic Parameters | Doses (mg) | | |
|----------------------------|---------------|---------------|----------------|
| | 50 (n = 7) | 70 (n = 7) | 100 (n = 7) |
| C_{max} (mg/L) | 2.52 (14.9) | 2.91 (23.7) | 3.83 (15.0) |
| AUC_{0-inf} (mg*h/L) | 53.3 (14.7) | 69.4 (18.9) | 105 (15.6) |
| CL (L/h/kg) | 0.0128 (10.9) | 0.0136 (12.6) | 0.0128 (9.4) |
| V_{ss} (L/kg) | 0.53 (12.9) | 0.57 (13.2) | 0.51 (10) |
| $t_{1/2}$ (h) | 39.3 (8.5) | 45.6 (10.3) | 42.3 (14.8) |

The elimination half-life of the drug varied between studies and ranged between 26 – 40 hours.

Figure XBAE 5.7.1. Mean LY303366 Plasma Concentrations following 0.1, 0.2, 0.5 and 1.0 mg/kg (Groups A and B) intravenous infusion over approximately 20 minutes (Cartesian scale for left panel and Semilogarithmic for right panel).



The PK parameters in patients estimated using the population approach, upon administration of a 100 mg loading dose followed by 50 mg maintenance dose is given below:

| | |
|---------------------|-----|
| C_{ss} (mg/L) | 3.5 |
| AUC_{ss} (mg*h/L) | 55 |

| | |
|------------------------|--------|
| CL (L/h/kg) | 0.0142 |
| V _{ss} (L/kg) | 0.7 |
| t _{1/2} (h) | 25.5 |

b) is this a high extraction ratio or a low extraction ratio drug?

Anidulafungin is a low extraction drug.

c) does mass balance study suggest renal or hepatic the major route of elimination?

The mass balance study indicated that the renal and hepatic routes of elimination are not significant. The major route of elimination of anidulafungin is chemical degradation followed by biliary excretion.

5. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The interindividual variability of the pharmacokinetic parameters was low (<30). The intersubject variability (%CV) for C_{max} ranged from 11% to 27% in Study XBAE and from 8% to 16% in Study 101L. The intersubject variability (%CV) for AUC ranged from 7% to 19% in Study XBAE and from 7% to 13% in Study 101L.

C. Intrinsic Factors

1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

The applicant performed a population pharmacokinetic analysis based on 600 Anidulafungin concentrations from 225 patients across 4 clinical trials (VER002-4, VER002-6, VER002-7 and VER002-11). The objectives of the analysis were to identify potential clinically significant factors for dose adjustment and to determine the sources of variability in anidulafungin pharmacokinetics to explain the various plasma profiles of anidulafungin in different patients for safety and efficacy concerns. The population PK analysis was reviewed by Dr. Yaning Wang, the pharmacometrics reviewer (see Appendix C for complete review). Based on the results of the analysis, recommendations for dosage-adjustment are given below:

2. Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups (examples shown below)? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

a) elderly

No systematic analysis of the differences in PK between elderly and young subjects was performed. However, because anidulafungin is not renally eliminated, dosage adjustments in elderly subjects are not necessary.

b) pediatric patients; Also- what is the status of pediatric studies and/or any pediatric plan for study?

Safety and effectiveness in pediatric patients and adolescents less than 18 years of age have not been established.

c) gender

No dosage adjustment of anidulafungin is required based on gender. Plasma concentrations of anidulafungin in healthy men and women were similar. In multiple-dose patient studies, drug clearance was slightly faster (approximately 22%) in men versus women.

d) race, in particular differences in exposure and/or response in Caucasians, African-Americans and/or Asians

No dosage adjustment of anidulafungin is required based on ethnicity. Anidulafungin pharmacokinetics were similar among Whites, Blacks, Asians, and Hispanics.

e) renal impairment

No significant changes in the pharmacokinetics of anidulafungin have been observed in studies of patients with various renal function. No dosage adjustments for patients with renal impairment are recommended by the applicant and this is acceptable.

f) hepatic impairment

No significant changes in the pharmacokinetics of anidulafungin have been observed in studies of patients with various liver function. No dosage adjustments for patients with hepatic impairment are recommended by the applicant and this is acceptable.

g) what pregnancy and lactation use information is there in the application?

There are no adequate and well-controlled studies in pregnant women. Anidulafungin should be used during pregnancy only if the potential benefit justifies the risk to the fetus. In animal studies, no selective reproductive toxicities were observed. Anidulafungin did not produce any developmental (embryo/fetal toxicity, teratogenicity) toxicity in rats at the highest dose tested, 20 mg/kg/day (8 times the human exposure provided by a 50 mg dose on a relative AUC basis). At a maternally toxic dose of 20 mg/kg/day, incomplete ossification of the metacarpals, and fetal weight depression occurred in rabbits (4 times the human exposure provided by a 50 mg dose on a relative AUC basis). Anidulafungin crossed the placental barrier in rats and was detected in fetal plasma.

h) other factors that are important to understanding the drug's efficacy and safety
No dosage adjustment of anidulafungin is required based on HIV status, irrespective of concomitant anti-retroviral therapy. Anidulafungin pharmacokinetics in HIV-infected subjects were similar to those observed in non HIV-infected subjects.

D. Extrinsic Factors

1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

No systematic analysis of the effect of the above-mentioned factors was conducted.

2. Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

Not Applicable

3. Drug-Drug Interactions

- a) is there an in vitro basis to suspect in vivo drug-drug interactions?
There is no in vitro basis to suspect in vivo drug-drug interactions.
- b) is the drug a substrate of CYP enzymes?
The drug does not appear to be a substrate of CYP enzymes
- c) is the drug an inhibitor and/or an inducer of CYP enzymes?
The drug does not appear to be an inhibitor or inducer of CYP enzymes.
- d) is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?
The applicant did not evaluate if anidulafungin is a substrate or an inhibitor of P-glycoprotein.
- e) are there other metabolic/transporter pathways that may be important?
There is no evidence to suggest that other metabolic/transporter pathways are important.
- f) does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?
The label does not specify co-administration with another drug.
- g) what other co-medications are likely to be administered to the target patient population?

The target population with esophageal candidiasis may be co-administered other drugs to treat HIV infection/AIDS. However, no interaction is expected based on the results of in vitro drug metabolism and the population PK analysis.

h) are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered? There are no in vivo drug-interaction studies to indicate differences in exposure.

i) is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There is no known mechanistic basis for drug-drug interactions, since anidulafungin is not metabolized by renal or hepatic pathways.

j) are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

There are no unresolved issues related to metabolism, active metabolites and protein binding.

E. General Biopharmaceutics

1. Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Not Applicable (Anidulafungin is formulated as an IV infusion.)

F. Analytical Section

1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The plasma samples from the initial human PK studies were analyzed by a validated high performance liquid chromatographic (HPLC) procedure with either fluorescence detection (Studies XBAE, XBAU, XBAA and XBAB) or ultraviolet (UV) detection at 300 nm (Studies 101L, XBAW, VER002-1, VER002-2, VER002-3, and VER002-5). Plasma samples from studies VER002-8 and VER002-10 and all the samples used for population PK analysis were analyzed using a validated liquid chromatographic tandem mass spectrometric (LC/MS/MS) procedure. Urine samples were analyzed by a validated HPLC procedure with fluorescence detection.

2. Which metabolites have been selected for analysis and why?

Not Applicable

3. What bioanalytical methods are used to assess concentrations?

a) what is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Please see below for a table that shows the comparison of assay parameters

b) what are the lower and upper limits of quantification (LLOQ/ ULOQ)?

Please see below for a table that shows the comparison of assay parameters

c) what is the accuracy, precision and selectivity at these limits?

| Assay | HPLC-Fluorescence | HPLC-UV | LCMS |
|----------------------|-------------------|-----------------|--------------------|
| Calibration Range | 5 – 1000 ng/mL | 20 – 5120 ng/mL | 101 – 20,165 ng/mL |
| Inter-assay Accuracy | 98.5 – 109.8% | 95.5 – 101% | 101 – 104% |
| Precision | 3.3 – 12.2% | 1.33 – 11.6% | 3.2 – 13.4% |
| Recovery | 59 – 64% | 80.23 – 82.3% | Not Available |
| Internal Standard | LY306168 | LY306168 | Efavirenz |

d) what is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Anidulafungin was found to be stable in plasma when stored frozen at -20°C or -70°C for [] without significant deterioration after successive freeze-thaw cycles. Some deterioration was observed for samples stored at room temperature and at [] after 24 hours.

Appears This Way
On Original

Appendix A. Individual Study Reviews (Available upon request)

Appears This Way
On Original

Appendix B. Pharmacometrics Review
Pharmacometrics Review
Office of Clinical Pharmacology and Biopharmaceutics

| | |
|---------------------------|--|
| NDA: | 21-632 |
| Volume: | |
| Compound: | Anidulafungin |
| Submission Dates: | 06/05/03 |
| EDR file names: | |
| Sponsor: | Vicuron Pharmaceuticals Inc. |
| Type of submission: | PM consult/Population Pharmacokinetic Analysis |
| Pharmacometrics Reviewer: | Yaning Wang, Ph.D. |
| Primary Reviewer: | Dakshina Chilukuri, Ph.D. |
| Date of Report: | |

| | |
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Executive Summary

A population pharmacokinetic analysis was performed for Anidulafungin (NDA 21-632) following intravenous infusion. Six hundred Anidulafungin concentrations from 225 patients across 4 phase II and III clinical trials were used for this analysis. The objectives of this analysis were:

- Identify potential clinically significant factors for dose adjustment
- Determine the sources of variability in Anidulafungin's pharmacokinetics to explain the various plasma profiles of Anidulafungin in different patients for safety and efficacy concerns

A mathematical model was developed to describe Anidulafungin plasma concentrations for these patients. The results of the analysis showed:

- Patient body weight, gender, and the effect of being in one specific study (Study VER002-6 where the patients had invasive candidiasis) were identified to be statistically significant predictors for the variability in the clearance of Anidulafungin, but together they only accounted for less than 20% of the overall variability in clearance and therefore may be deemed to be of little clinical significance.
- The presence of metabolic substrates, metabolic inhibitors, metabolic inducers, or rifampin had no effect on the clearance of Anidulafungin.
- The data in the 4 clinical studies (mainly sparse samples) used in this analysis only supported 34.9% between-subject variability in the clearance of Anidulafungin. Less than 20% of this overall variability could be explained by patient body weight, gender and whether the patients were in Study VER002-6 and the rest of it could be due to random between-subject variability or controlled by other unknown factors. Proportional random residual error (24%) also contributed to the variability in plasma concentrations of Anidulafungin in different patients.

Recommendation:

The sponsor's claim about the pharmacokinetic similarity of Anidulafungin between HIV positive and negative patients should be adjusted to show the limitations in the data.

Introduction

Summary

This NDA (21-632) submission is seeking approval for Anidulafungin. Anidulafungin is a novel compound that has been evaluated as a potential treatment for esophageal candidiasis. Anidulafungin is a member of a new class of antifungal drugs whose antifungal effects are believed to result from selective inhibition of the synthesis of glucan, an essential component of fungal cell walls. It is being developed as a sterile, lyophilized product for intravenous (IV) infusion.

Anidulafungin is rapidly and extensively distributed following IV infusion. The volume of distribution is 30 - 50 L, similar to the whole body fluid volume. Plasma concentrations and exposures of Anidulafungin are dose-proportional and have low intersubject variability (coefficient of variation <25%). Using a loading dose on day 1 that is twice the daily maintenance dose, steady state is achieved following the second dose. Anidulafungin has a half-life of approximately 1 day that characterizes the majority of the plasma concentration-time profile. Anidulafungin is moderately protein bound (84%) in humans. Anidulafungin is slowly chemically degraded at physiologic temperature and pH to a ring-opened peptide that lacks antifungal activity. The ring-opened peptide is subsequently degraded and eliminated. Anidulafungin and its degradation products are eliminated in feces. Anidulafungin is not excreted in urine. Plasma clearance of Anidulafungin is approximately 1 L/hour and is dose independent. Repeated dosing does not influence distribution or clearance. Greater than 90% of the drug is eliminated as small tertiary degradation products in feces. A small amount of intact drug (<10%) and negligible amount of ring-opened product were observed in feces.

In the treatment of esophageal candidiasis in clinical studies, Anidulafungin was shown to be at least as effective as fluconazole (97.2% versus 98.8%) based on the proportion of patients with a successful endoscopic response at the end of therapy. At the 2 week follow-up visit, however, sustained endoscopic success was observed in 64.4% and 89.5% of patients treated with Anidulafungin and fluconazole, respectively. There was no emergence of resistance to Anidulafungin in any clinical study.

The sponsor performed a population pharmacokinetic analysis of intravenous Anidulafungin based on 600 Anidulafungin concentrations from 225 patients across 4 phase II and III clinical trials. A two-compartment model with first order elimination was found to be the structural model with the clearance being influenced by weight, gender, and the effect of being in Study VER002-6. Inter-patient variability in the central volume of distribution was not supported in the model. However, weight was determined to be a predictor of the central volume of distribution. Inter-patient variability in CL was estimated to be 28%. Although weight, gender, and the effect of being in Study VER002-6 were identified as sources of variability in CL, together they accounted for less than 20% of the overall variability and therefore may be deemed to be of little clinical relevance. The presence of metabolic substrates, metabolic inhibitors, metabolic inducers, or rifampin had no effect on the clearance of Anidulafungin. The results were used to support the sponsor's claim that no dosage adjustments were required for geriatric status,

gender, weight, ethnicity, disease status, hepatic impairment, renal impairment, and concomitant medications.

Objective of the analysis

- Identify potential clinically significant factors for dose adjustment
- Determine the sources of variability in Anidulafungin's pharmacokinetics to explain the various plasma profiles of Anidulafungin in different patients for safety and efficacy concerns

Methods

Objectives and Assumptions

Objectives

- Develop the population pharmacokinetic model for Anidulafungin after intravenous infusion
- Determine the statistical significance of possible covariates on the population pharmacokinetic parameters
- Estimate the intersubject variability of the pharmacokinetic parameters and the random residual error

Assumptions

- The same pharmacokinetic structural model applies to all the patients
- All the individual pharmacokinetic parameters follow log-normal distribution
- The errors in the residual error model follow normal distribution with mean 0 and independent
- The concentration measurements at different time points are independent
- The measurements of time and covariates are error-free

Study Design/Data

The sponsor performed this population pharmacokinetic analysis based on 600 Anidulafungin concentrations from 225 patients across 4 clinical trials (VER002-4 (PK), VER002-6, VER002-7, and VER002-11). The study design and pharmacokinetic sampling schedule for each study is presented in Table 1. Table 2 listed the summary of the demographic information and other potential covariates.

Table 1. Designs of the Four Studies Included in the Population PK analysis

| Study | Patients (n) | Dosing regimen | Sampling |
|---------------|------------------------------|------------------------------------|---|
| VER002-4 (PK) | esophageal candidiasis (129) | 100/50mg | Day 3: Post-dose Day 7: Pre-dose Day 14: Delayed post-dose Day 21 Pre-dose |
| VER002-6 | invasive candidiasis (87) | 100/50 , 150/75 , or 200/100 mg | Day 3: Post-dose Day 6: Pre-dose Day 13: Delayed post-dose |

| | | | |
|-----------|--|---------------------------|--|
| | | | Day 20: Pre-dose |
| VER002-7 | invasive aspergillosis (7) | 200/100mg with AmBisome®. | Similar to VER002-4 (PK) |
| VER002-11 | fluconazole refractory mucosal candidiasis (2) | 100/50mg | Day 1: Pre-dose Day 7: Pre-dose, 30 minutes after the start of infusion, at the end of infusion, 15, 30, and 60 minutes after the end of infusion, and 3, 6, 12, and 24 hours after the start of infusion Day 14: Pre-dose |

Since the sponsor did not submit the original data and the code for constructing the data to NONMEM format (although this was requested), only visual inspection of plots was conducted for the final NONMEM data (VES00100_NM2.csv).

Modeling and Simulation

The sponsor initially established the structural (compartmental) and statistical (variability) models without the inclusion of covariates.

Software

The sponsor developed the population pharmacokinetic model by applying a non-linear mixed-effects modeling approach with First Order (FO) and First Order Conditional Estimation with Interaction (FOCEI) maximum likelihood estimation in the NONMEM program (double precision, Version V, Level 1.1) and NM-TRAN pre-processor. Models were compiled using Compaq Visual Fortran (Version 6.6) and were run via PDx-Pop (Version 1.1j) under the Windows NT4 operating system. All figures were created using SPlus2000 for Windows. The reviewer evaluated the results by applying the same versions of NONMEM and Compaq Visual Fortran except via WINGS for NONMEM (Version 404) under the Windows 2000 professional operating system.

Structural Model

The sponsor explored one- and two-compartment linear models in fitting the Anidulafungin plasma concentration data. The models were parameterized in terms of clearance (CL), central volume of distribution (V1), intercompartmental clearance (Q), and peripheral volume of distribution (V2).

The sponsor developed the initial structural model by using the First Order (FO) estimation method in NONMEM and refined the base model with the First Order Conditional Estimation with Interaction (FOCEI) method in NONMEM once an appropriate base model was chosen.

The following criteria were applied by the sponsor to select the appropriate base population pharmacokinetic model:

- a significant reduction in the objective function value ($p < 0.05$);
- decrease in the residual error and in some cases, the standard error of the model parameters;
- randomness of the individual weighted residuals distribution against the predicted concentration and time;
- randomness of the observed concentration distribution *versus* individual predicted concentration values across the identity line

Random Variance Models

The sponsor utilized an exponential error model to describe the between-subject variability in all pharmacokinetic parameters, e.g., for CL:

$$CL_j = CL_{0j} \exp(\eta_{jCL}), \text{ (Eq. 1)}$$

where $\exp(\eta_{jCL})$ denoted the difference (proportional) between the true individual parameter (CL_j) and the typical value (CL_{0j}) predicted for an individual with covariates equal to those of patient j . In the base model without covariates, CL_{0j} is the same for all individuals, and it was denoted by CL_0 . Inter-patient variability was modeled the same way for the other parameters. The individual random effects, η 's (e.g., η_{jCL}), are random variables following normal distribution with a mean of zero and variances of ω^2 (e.g., ω^2_{CL}). Models with the diagonal and full variance-covariance matrix (Ω) of between-subject random effects were evaluated.

The sponsor modeled the residual variability with a combined additive and constant CV error model:

$$Y_{ij} = F_{ij} + F_{ij} \varepsilon^P_{ij} + \varepsilon^A_{ij}. \text{ (Eq. 2)}$$

Y_{ij} and F_{ij} were the i th measured and model predicted plasma concentrations for the j th patient, respectively. The parameters ε^P_{ij} and ε^A_{ij} denoted the random residual error for the constant coefficient of variation (CV) and additive portion of the error, respectively.

Both of them were assumed to follow normal distributions. Means of all the residual error terms were assumed to be equal to zero; variances were denoted as σ^2_P and σ^2_A , respectively. The random variables ε^P_{ij} and ε^A_{ij} were assumed to be independent. The independency between ε^P_{ij} and $\varepsilon^P_{i'j'}$ where $i \neq i'$ or $j \neq j'$ was assumed even though the sponsor did not explicitly mention it. The same assumption was also taken for ε^A_{ij} .

Covariate Model

The sponsor explored for influential prognostic factors from demographic data (age, weight, gender, and race), presence of concomitant medication categories (metabolic substrates, metabolic inducers, and metabolic inhibitors), presence of rifampin and different studies (VER002-4 (PK), VER002-6, VER002-7, and VER002-11).

Continuous covariates were entered into the model according to equation 3:

$$P = \theta_1 + \theta_2 \cdot (COV - \overline{COV}) \text{ (Eq. 3)}$$

where:

P is the individual estimate of the parameter obtained by empirical Bayesian estimation in NONMEM.

θ_1 represents the typical value of the parameter (when $COV = \overline{COV}$)

θ_2 represents the slope of the effect of the covariate on the parameter (for example, body weight or age)

COV is the value of the covariate

\overline{COV} is the median value of the covariate in the study population

Categorical covariates were included in the model using indicator variables as shown in equation 4:

$$P = \theta_1 + \theta_2 \cdot IND \text{ (Eq. 4)}$$

Where:

P is the individual estimate of the parameter

θ_1 represents the typical value of the parameter when $IND = 0$

θ_2 represents the effect of the covariate (when $IND = 1$)

IND is an indicator variable, which has a value of 1 when the covariate is present, otherwise $IND = 0$

The relationships between covariates and individual pharmacokinetic parameters were explored graphically and via Generalized Additive Modeling (GAM) analysis in Xpose (A population model building aid for NONMEM using SPLUS). The sponsor built an initial "full" model by incorporating all of the covariates that were significant based on Akaike Information Criteria (AIC) values from the GAM analysis and then used a backward elimination process to evaluate the significance of each covariate in the "full" model. The criteria applied by the sponsor to remove a covariate from the model were the minimum objective function (MOF) did not increase by more than 10.83 (χ^2 , $p < 0.001$; $df=1$) and no substantial increase occurred in the corresponding random effect parameter. After the final model was built, the sponsor tested the possible influence of patient HIV status and the diluent used to reconstitute drug product on the final model.

Final Model Evaluation

The sponsor evaluated the ability of the final Anidulafungin population PK model to describe the observed data by using Monte Carlo simulations in NONMEM. The final Anidulafungin population PK model, including final fixed effect parameters and random effect parameters (between-subject variability and residual error) were used to create 100 replications of the observed PK data set. The sponsor calculated the 90th, 80th, 50th (median), 20th and 10th quantiles of the simulated data for each time point and plotted them against the observed data to show that the majority of observed data fell within the boundaries of the 90th and 10th quantiles of the simulated data, suggesting that the observed data could be accurately described by the derived population PK model.

Results

Data Integrity

Plots of the concentrations versus absolute sampling times showed inconsistency between the data and the protocol. In the protocol for study VER002-4 (PK), the sampling scheme was presented as follows:

Day 3: Post-dose (0-4 hours following the end of infusion)

Day 7: Pre-dose

Day 14: Delayed post-dose (ideally 8-12 hours following the end of infusion)

Day 21 Pre-dose (if patient remains on study therapy)

But the plot (Figure 1) showed that all the samples on day 7 and day 21 are post-dose samples. Based on the protocol, those samples should be post-dose samples relative to day 6 and day 20. Since the sponsor treated all the samples as steady state concentrations, the modeling output should not be affected by this inconsistency as long as the post-dose times were correctly calculated relative to day 6 and day 20. However, it is believed to be a coding error during NONMEM data construction. The same situation happened for study VER002-6 and study VER002-7 but not for study VER002-11.

Model and Model Selection

Model description

Two-compartment model was found to best fit the data. The data did not support the estimation of between-subject variability for any pharmacokinetic parameters but CL. Weight, gender and being in study VER002-6 were found to be statistically significant covariates for CL and weight was also a significant covariate for V1. The covariate models for CL and V1 were described by equation 5 and 6.

$CL (L/h) = 0.768 + 0.00417*(WT-60kg) + 0.166*Gender + 0.278*Study$ (Eq. 5)
(Gender = 1 for male and 0 for female and Study = 1 for VER002-6 and 0 for all others)

$V1 (L) = 0.215 * WT$ (Eq. 6)

Parameter estimation results

The parameter estimates, their estimation precision, between-subject variability and residual error were tabulated in Table 3.

Goodness of fit

The diagnostic plots shown in Figure 2 and Figure 3 demonstrated the goodness of fit of the final population pharmacokinetic model for the observed Anidulafungin concentrations.

Model Selection

Two-compartment model was found to fit the data significantly better than one-compartment model. During the base model development, the sponsor first removed the between-subject variability for V1 and V2 (Model 101) because the estimates from FO

method were approximately zero with poor precision (%RES>1000%). The reduced model was justified by the insignificant change in MOF (Table 4). When FOCEI method was used and failed to generate the covariance output, the sponsor believed that the model (Model 007) might be over-parameterized or might be at a local minimum (I think the sponsor really meant to state “may be at a local minimum” even though “may not be at a local minimum” was written in the report) and therefore removed the between-subject variability for Q. The sponsor justified this step by stating that the between-subject variability on Q was very high as demonstrated by a %CV of 89.6%. The reviewer conducted a simulation at two different scenarios (Table 6), assuming known between-subject variability for V1 and V2 at two levels. The first level of between-subject variability for V1 and V2 (Table 5) were obtained by fitting the data pooled from 5 phase 1 studies (101L, XBAE, XBAU, VER002-1 and VER005-5) with Model 003H. Since the between-subject variability for CL estimated for healthy volunteers (Table 5) was only half of that for patients, a higher level (twice the first level) of between-subject variability for V1 and V2 was also tested. The simulated data were fitted with Model 101 to evaluate the impact of fixing the between-subject variability for V1, V2 and Q to zero on the estimation of CL and its between-subject variability. The sponsor further removed the additive error term (Model 222) because it was poorly estimated and might not be necessary in the residual error model. The impact of this step was also evaluated by fitting the simulated data with Model 222 (Table 6). Model 222 was chosen by the sponsor as the base model and only CL had a between-subject variability term.

The sponsor fitted Model 222 with two alternative parameterizations to confirm that the data supported between-subject variability only on CL or its reparameterized alternative. The reviewer reevaluated one of the two alternative parameterizations (Table 7).

For the covariate model building, weight was tested for potential covariate for V1 and V2 despite the lack of between-subject variability on V1 and V2 in the base model (Model 222). Based on the GAM screening results, weight, gender and study were incorporated into the “full” model as potential covariates for CL via a linear equation. Due to the convergence problem, certain restrictions was put on the covariate model for V1, resulting in a simple intercept model without centering (Model 309). The final model (Model 404) was obtained after the backward elimination process (Table 8). Patient HIV status, the presence of concomitant medications, such as metabolic substrate (SUB), metabolic inducers (IND), or metabolic inhibitors (INH), the presence of rifampin (RIF) and the diluent (DIL) used for reconstitution (water or ethanol) were tested on the final model and none was found to be significant (Table 8).

Model Evaluation

The sponsor calculated the 90th, 80th, 50th (median), 20th and 10th quantiles of the 100 sets of simulated data for each time point and plotted them against the observed data (Figure 4). The majority of observed data fell within the boundaries of the 90th and 10th quantiles of the simulated data, suggesting that the observed data could be accurately described by the derived population PK model.

Discussion

The significance of the results

The sponsor claimed that no dosage adjustments were required for geriatric status, gender, weight, ethnicity, HIV status and concomitant medications based on the results of this analysis.

The validity of the results

In general the results of the analysis are valid. However the impacts of certain restrictions applied by the sponsor during the model development process on the final results should have been evaluated.

1. The removal of the between-subject variability on Q

Why is high between-subject variability the reason to remove it? What is the impact of this step on the estimation of CL and its between-subject variability? The reviewer conducted a simulation to evaluate this impact. The results (Table 6) indicated that the impact is minimal for the estimation of CL and its between-subject variability even though the estimation of V1, V2 and Q were affected.

2. The removal of the additive error term in the residual error model

Considering the samples were all taken at steady state and most of them (minimum 0.34 mg/L) were far above the limit of quantification of the analytical assay (0.1mg/L), it is reasonable to state that the proportional error term was sufficient and the additive error term was not necessary. The impact of this step on the estimation of CL and its between-subject variability was shown to be minimal based on simulation results (Table 6).

An alternative to fixing parameters to zero is to add more data for model fitting. Only 4 out of 14 studies with PK data were used for this analysis. The data from other studies, especially two phase II studies (XBAF n=36 and XBAG n=3), may release some of the restrictions exerted by the sponsor due to the lack of information about certain parameters in those 4 studies.

3. Clinical significance of the statistically significant covariates

Even though weight, gender and being in Study VER002-6 were found to be statistically significant covariates for CL, the sponsor claimed that they were not clinically relevant since less than 20% of between-subject variability (34.9%) in CL was explained by them.

4. Non-significant effect of HIV status on CL

Given the distribution of HIV status in the database (i.e., N = 184 (82%) HIV test not performed, N= 10 (4%) HIV negative, and N = 31 (14%) HIV positive), the reliability of the non-significant results is questionable. The large percentage of non-tested HIV status, which is in fact a mixture of HIV negative and HIV positive with a ratio that is likely to be approximately 4%:14%, indicated that the overall effect of HIV status was

dominated by a mixed effect of HIV negative and HIV positive. This could be the reason for the non-significance. However, given the relatively simple Anidulafungin elimination pathway, mainly chemical degradation, the impact of HIV status on CL may not be clinically relevant.

Overall Conclusions

1. Are there any clinically relevant covariates for dose adjustment?

Although weight, gender, and the effect of being in Study VER002-6 were identified as sources of variability in CL, together they accounted for less than 20% and therefore may be deemed to be of little clinical significance.

The presence of metabolic substrates, metabolic inhibitors, metabolic inducers, or rifampin had no effect on the clearance of Anidulafungin.

Therefore, no clinically relevant covariates for dose adjustment were identified.

2. What are the major sources of variability in Anidulafungin's pharmacokinetics to account for the various plasma profiles of Anidulafungin in different patients?

The data in the 4 clinical studies (mainly sparse samples) used in this analysis only supported 34.9% between-subject variability in the clearance of Anidulafungin. Less than 20% of this overall variability could be explained by patient body weight, gender and whether the patients were in Study VER002-6 and the rest of it could be due to random between-subject variability or controlled by other unknown factors. Proportional random residual error (24%) also contributed to the variability in plasma concentrations of Anidulafungin in different patients.

Recommendations

Pharmacometrics Labeling Comments

CLINICAL PHARMACOLOGY; *Special Populations*

HIV Status

No dosage adjustment of Anidulafungin is required based on HIV status, irrespective of concomitant anti-retroviral therapy. Anidulafungin pharmacokinetics in HIV-infected subjects were similar to those observed in non HIV-infected subjects.

Proposed Revision:

HIV Status

No dosage adjustment of Anidulafungin is required based on HIV status, irrespective of concomitant anti-retroviral therapy.

C

J 1. A direct comparison of the results from HIV infected patients and non-HIV infected patients is needed to support such a statement.

General Comments Not to be Sent to Sponsor

- In the analyses, the sponsor should have constructed the data based strictly on the study protocols even though the outcome would not be affected for steady state sampling if the actual dosing dates were not correctly used under certain circumstances.
- The sponsor should have evaluated the impact of removing the between-subject variability for Q on the estimation of the between-subject variability for CL.
- Even though the sponsor listed the results from alternative parameterized models, the data supported the between-subject variability only for CL. However, the reviewer found that if the model was parameterized in K, V1, K12 and K21, the model with V1 bearing all the between-subject variability would be significantly better than the model proposed by the sponsor based on objective function value. The sponsor should have shown the intermediate steps to help clarify the conflicting results.
- The sponsor should have explained why the full model could identify weight as a significant covariate for V1 while the base model did not support the between-subject variability for V1.
- The sponsor should be consistent with the terminology. For example, MOF (minimum objective function) was used in the text but OFV (not defined in the Glossary of Abbreviations) was used in Table 6.1.7.

_____ Date: _____
Yaning Wang, Ph.D.
Pharmacometrics Reviewer
Office of Clinical Pharmacology/Biopharmaceutics

Concurrence: Phil Colangelo, Pharm.D, Ph.D. (TL) _____ Date: _____

3 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Appendix B

Exploratory Exposure/Response Analysis for Relapse Rate in Study VER002-4

Introduction

The pivotal study, VER002-4, was conducted to determine whether anidulafungin is at least as effective as fluconazole in the treatment of esophageal candidiasis.

The sponsor defined the primary endpoint used to assess the non-inferiority of anidulafungin vs. fluconazole as endoscopic response at the end of therapy (EOT) in the clinically evaluable at EOT population. The results showed that the endoscopic success rate in the anidulafungin group was 97.2% and in the fluconazole group was 98.8%, with an associated 95% CI of the treatment difference of (-4.1%, 0.8%). Thus, the lower bound of the CI for the difference in success was > -10%, indicating that anidulafungin was non-inferior to fluconazole in endoscopic success at EOT. However, the endoscopic response at follow-up (FU), the secondary efficacy endpoint, indicated a statistically significant lower persistent success rate in the anidulafungin group (64.4%) than in the fluconazole group (89.5%). The sponsor did not provide reasonable explanation for this higher relapse rate for anidulafungin. The reviewer, therefore, tried to explore the possible reason for the higher relapse rate for the anidulafungin group.

Method

A logistic regression model (Eq. 7) was applied to explore the relationship between individual PK metrics and the relapse status (1 for relapse, 0 for persistent success) at FU for the patients in the anidulafungin group.

$$\log \frac{p}{1-p} = \beta_0 + \beta_1 \cdot X \quad (\text{Eq. 7})$$

where p is the relapse rate and X is a PK metric.

The studied PK metrics included the steady state AUC (AUC_{ssi}) and the trough concentration (C_{troughi}). The individual AUC_{ssi} was obtained according to equation 8:

$$AUC_{ssi} = \frac{DOSE_i}{CL_i} \quad (\text{Eq. 8})$$

where DOSE_i is the maintenance dose for individual i and CL_i is the empirical Bayesian clearance estimate for individual i . The concentration at approximately 24 hour on day 7 (NONMEM data file) was taken as the individual C_{troughi}. Only those patients who had endoscopic success at EOT and also PK metrics were included in the analysis. Those patients with indetermined status at FU were either treated as relapse or removed for the analysis. The PROC LOGISTIC in SAS (Version 8.02) was used for the analysis. PK metrics were treated as continuous variables and grouping was not conducted. PK metrics on original scale and log-transformed scales were both tried as the explanatory variable.

Results and Discussion:

The results (Table 9) indicted no statistically significant relationship between AUC_{ssi} or C_{troughi} with the relapse rate. Even though AUC_{ssi}/MIC (minimum inhibitory concentration) or C_{troughi}/MIC was believed to be more reasonable PK metrics for exposure/response correlation, the lack of an established method to measure MIC for *C. albicans*, the cause for the majority of cases of esophageal candidiasis, invalidated the application of MIC for any clinically relevant purpose.

Conclusion:

No statistically significant relationship was found between AUC_{ssi} or C_{troughi} and the relapse rate at FU for patients in anidulafungin group.

Table 2 Summary of Patients Demographics and Other Potential Covariates

| Covariate | Median (range) - or - Count (%) |
|-----------------------------|---------------------------------------|
| Weight (kg) | 60 (31 – 154) |
| Age (y) | 42 (18 – 88) |
| Gender (male/female) | 107 (48%)/118 (52%) |
| Race\Ethnicity | |
| Caucasian | 91 (40%) |
| Black | 26 (12%) |
| African American | 29 (13%) |
| Asian | 41 (18%) |
| Mixed, Russian, or Hispanic | 38 (17%) |
| Metabolic Substrates | |
| Metabolic Inhibitors | 204(91%) |
| Metabolic Inducers | 140(62%) |
| Rifampin | 40(18%) |
| | 27(12%) |
| HIV Status | |
| HIV test not performed | 184 (82%) |
| HIV negative | 10 (4%) |
| HIV positive | 31 (14%) |
| Diluent | |
| Water | 197 (87%) |
| Ethanol | 28 (12%) |

Table 3: Anidulafungin Final Population Model Parameter Estimates

| Anidulafungin Final Model Parameter Estimates – FOCEI Method | | |
|--|---|---------------------------|
| Structural Model and Inter-patient Variance Parameters | | |
| Parameter | Typical Value (%RSE*) | Inter-patient %CV (%RSE*) |
| CL (L/h) | CL = $\theta_1 + (WT - MWT)*\theta_5 +$ GENDER* $\theta_6 +$ STUDY* θ_7 | 28.0% (17.6%) |
| θ_1 | 0.768 (3.80%) | - |
| θ_5 | 0.00417 (26.9%) | - |
| θ_6 | 0.166 (25.4%) | - |
| θ_7 | 0.278 (20.8%) | - |
| V1 (L/kg) | V1 = $\theta_2 * WT$ | NS |
| θ_2 | 0.215 (20.3%) | - |
| Q (L/h) | Q = θ_3 | NS |
| θ_3 | 20.3 (16.7%) | - |
| V2 (L) | V2 = θ_4 | NS |
| θ_4 | 19.6 (15.1%) | - |
| V _{ss} (L) | 33.4** | 14.3%*** |
| T _{1/2} (h) | 25.6** | 29.1%*** |
| Residual Error | | |
| Parameter | Estimate (%RSE*) | |
| σ^2_{prop} | %CV= 24.0% (9.69%) | NA |

**RSE: percent relative standard error of the estimate = SE/parameter estimate * 100 (for variability terms this is the %RSE of the variance estimate)

**Calculated from individual parameter values: $T_{1/2} = \text{Log}(2)/(0.5*((K+K_{12}+K_{21})-\text{SQRT}((K+K_{12}+K_{21})-(4*K*K_{21}))))$, $V_{ss}=V_1+V_2$

***Calculated as (Standard Deviation /Mean)*100

Abbreviations: FOCEI = first order conditional estimation with interaction, CL = clearance, V1= central volume of distribution, Q = intercompartmental clearance, V2 = peripheral volume of distribution, V_{ss} = volume of distribution at steady-state, T_{1/2} = terminal phase half-life, σ^2_{prop} = proportional component of the residual error model, NS = Not Supported in Model, NA = Not Applicable, WT = weight (kg), MWT = 60 kg, GENDER = 1 for males and 0 for females; STUDY = 1 for VER002-6 and 0 for all other studies

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Table 4: Summary of NONMEM Runs to Define Anidulafungin Base Population Pharmacokinetic Structural Model

| Anidulafungin Base Structural Model Building - FO Method | | | | |
|--|---------------------|-------------------|---------|----------|
| Model # & Parameterization | Parameters with ISV | MOF | ΔMOF | |
| 001 | CL, V | CL and V | 688.216 | NA |
| 003 | CL, V1, Q, V2 | CL, V1, Q, and V2 | 611.516 | 76.7* |
| 005 | CL, V1, Q, V2 | CL, Q, and V2 | 611.516 | 0** |
| 006 | CL, V1, Q, V2 | CL, Q, and V1 | 611.523 | 0.007*** |
| 007 | CL, V1, Q, V2 | CL and Q | 611.523 | 0**** |

*change in MOF relative to Model 001

** change in MOF relative to Model 003

*** change in MOF relative to Model 005

**** change in MOF relative to Model 006

Abbreviations: FO = first order estimation, ISV = inter-patient variability, CL = clearance, V1 = central volume of distribution, Q = intercompartmental clearance, V2 = peripheral volume of distribution, NA = Not Applicable

Table 5: Anidulafungin Base Population Pharmacokinetic Parameter Estimates for Healthy Volunteers (Model 003H)

| Anidulafungin Base Model Parameter Estimates-FOCEI Method Structural Model and Between-subject Variance Parameters | | |
|---|---------------------------------|-----------------------------|
| Parameter | Typical Value (% RES*) | Between-Subject %CV (%RES*) |
| CL(L/h) | 0.992 (1.8) | 17.2 (16.4) |
| V1(L) | 20.3 (3) | 26.5 (13.9) |
| Q(L/h) | 1.95 (17.3) | 145.6 (7.1) |
| V2(L) | 18.3 (2.5) | 18.5 (17.3) |
| Parameter | Residual Error Estimate (%RES*) | |
| σ_1 | %CV=11.2% (6.1) | NA |
| σ_2 (mg/L) | 0.014 (28.3) | NA |

* %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100 (for variability terms this is the %RSE of the variance estimate)

Abbreviations: FOCEI = first order conditional estimation with interaction, CL = clearance, V1 = central volume of distribution, Q = intercompartmental clearance, V2 = peripheral volume of distribution, σ_1 = proportional component of the residual error model, σ_2 = additive component of the residual error model, NA = Not Applicable

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Table 6: The Impact of Certain Restrictions on The Estimation of CL and Its Between-subject Variability

| Parameter | Scenario 1 | | | | | Scenario 2 | | | | |
|-------------------|------------|--------|--------------|------|--------------|------------|------|--------------|------|--------------|
| | True* | Res1** | Fit1*** | Res2 | Fit2 | True | Res1 | Fit1 | Res2 | Fit2 |
| CL(L/h) | 0.946 | NA | 0.942 | NA | 0.944 | 0.946 | NA | 0.943 | NA | 0.949 |
| V1(L) | 9.97 | NA | 14.5 | NA | 14.4 | 9.97 | NA | 14.6 | NA | 15.0 |
| Q(L/h) | 24.2 | NA | 14.2 | NA | 14.4 | 24.2 | NA | 14.0 | NA | 13.2 |
| V2(L) | 23.2 | NA | 18.2 | NA | 17.9 | 23.2 | NA | 18.4 | NA | 18.0 |
| %CV _{CL} | 31.6 | NA | 31.6 | NA | 31.9 | 31.6 | NA | 31.2 | NA | 31.1 |
| %CV _{V1} | 26.5 | 0 | NS | 0 | NS | 52.9 | 0 | NS | 0 | NS |
| %CV _Q | 89.4 | 0 | NS | 0 | NS | 89.4 | 0 | NS | 0 | NS |
| %CV _{V2} | 18.5 | 0 | NS | 0 | NS | 37.4 | 0 | NS | 0 | NS |
| σ1(%) | 24.5 | NA | 24.8 | NA | 25.8 | 24.5 | NA | 25.7 | NA | 27.4 |
| σ2(mg/L) | 0.01 | NA | 0.16 | 0 | NS | 0.01 | NA | 0.21 | 0 | NS |

* True: the true values for parameters used for simulation

** Res1 or 2: restrictions applied by the sponsor

*** Fit1 or 2: Parameter estimates fitted under restriction 1 or 2 for the simulated data

Abbreviations: FOCEI = first order conditional estimation with interaction, CL = clearance, V1 = central volume of distribution, Q = intercompartmental clearance, V2 = peripheral volume of distribution, σ₁ = proportional component of the residual error model, σ₂ = additive component of the residual error model, NS = Not Supported, NA = Not Applicable

Table 7: Summary of NONMEM Runs to Develop Anidulafungin Base Population Pharmacokinetic Structural Model Based on Alternative Parameterization

| Anidulafungin Base Structural Model Building – FO Method | | | | |
|---|----------------|---------------------|---------|------------|
| Model # | Parameters | Parameters with BSV | MOF | ΔMOF |
| 003A | K, V, K12, K21 | K, V, K12, and K21 | 574.329 | NA |
| 003B | K, V, K12, K21 | K, V, and K12 | 574.329 | 0* |
| 003C | K, V, K12, K21 | V, K12, and K21 | 574.329 | 0* |
| 003D | K, V, K12, K21 | V and K12 | 574.329 | 0** |
| Anidulafungin Base Structural Model Building – FOCEI Method | | | | |
| 003E | K, V, K12, K21 | V and K12 | 484.809 | NA |
| 003F | K, V, K12, K21 | V | 485.701 | 0.892*** |
| FOCEI Method with Additive Error Term Removed | | | | |
| 003G | K, V, K12, K21 | V and K | 488.546 | NA |
| 003H | K, V, K12, K21 | V | 489.62 | 1.074**** |
| 226 | K, V, K12, K21 | K | 530.328 | 41.782**** |

*change in MOF relative to Model 003A

** change in MOF relative to Model 003B

*** change in MOF relative to Model 003E

**** change in MOF relative to Model 003G

Abbreviations: FO = first order estimation, BSV = between-subject variability, FOCEI = first order conditional estimation with interaction, K = elimination rate, K12 = central to peripheral rate, K21 = peripheral to central rate, MOF = minimum objective function

Table 8: Summary of NONMEM Runs for Covariate Model Breakdown

| Run No. | Parameter—Covariate | OFV | Decrease in OFV Relative to FULL Model | Significance (p< 0.001) |
|---|--------------------------------------|---------|--|----------------------------|
| FULL MODEL | | | | |
| 309 | CL~WT+GENDER+STUY6 V1~WT V2~WT | 422.723 | — | — |
| Step One - Model Breakdown* | | | | |
| 401 | CL~WT=0 | 436.233 | 13.51 | * |
| 402 | CL~GENDER=0 | 438.902 | 16.179 | * |
| 403 | CL~STUDY6=0 | 451.233 | 28.51 | * |
| 404 | V2~WT=0 | 423.577 | 0.854 | |
| 303 | V1~WT=0 | 430.023 | 7.3 | * |
| Step Two - Model Breakdown** | | | | |
| 405 | CL~WT & V2~WT=0 | 436.286 | 12.709 | * |
| 406 | CL~GENDER & V2~WT=0 | 439.703 | 16.126 | * |
| 407 | CL~STUDY6 & V2~WT=0 | 452.124 | 28.547 | * |
| 408 | V1~WT & V2~WT=0 | 445.426 | 21.849 | * |
| Step Three - Final Model Testing** | | | | |
| 409 | Model 404 + CL~SUB | 422.356 | -1.321 | |
| 410 | Model 404 + CL~INH | 423.181 | -0.396 | |
| 411 | Model 404 + CL~IND | 421.833 | -1.744 | |
| 412 | Model 404 + CL~RIF | 421.012 | -2.565 | |
| 415 | Model 404 + CL~DIL | 423.462 | -0.115 | |
| 416 | Model 404 + CL~HIV | 418.972 | -4.605 | |
| Final Population Model | | | | |
| 404 | CL~WT+GENDER+STUY6 V1~WT | 423.577 | — | — |

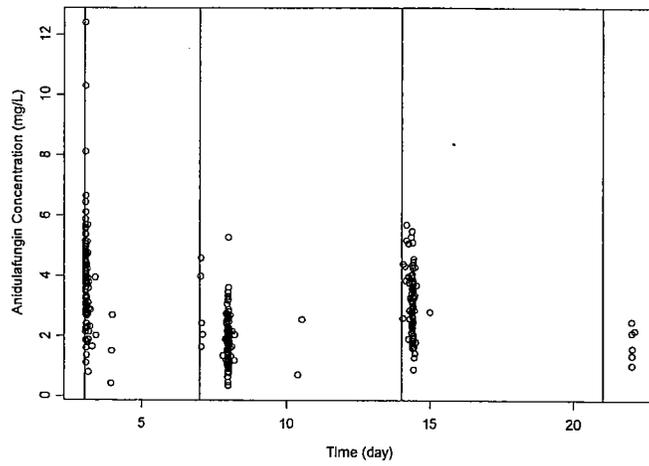
*Full model for Step One was Model 309

** Full model for Step Two and Step Three was Model 404

Table 9: Logistic regression analysis for PK metrics vs relapse rate

| PK metric | Treatment of Interdermined patients at FU | p-value ($\beta_1=0$) |
|-------------|---|----------------------------|
| AUCss | Relapse (n=115) | 0.2812 |
| | Removal (n=105) | 0.5615 |
| Log AUCss | Relapse (n=115) | 0.4276 |
| | Removal (n=105) | 0.8253 |
| Ctrough | Relapse (n=104) | 0.3561 |
| | Removal (n=95) | 0.5698 |
| Log Ctrough | Relapse (n=104) | 0.7108 |
| | Removal (n=95) | 0.9661 |

Figure 1: Plasma Concentrations vs Absolute Sampling Time for study VER002-4 (PK) (the vertical lines are at 3, 7, 14 and 21 days)



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Figure 2: Population Mean Predictions vs Observed Plasma Anidulafungin Concentrations (Final Model)

Population mean predictions, using the final model (FOCEI method), versus observed plasma Anidulafungin concentrations are indicated by individual ID numbers and a LOESS smooth of the data (dotted line). The line of identity (solid) is included as a reference.

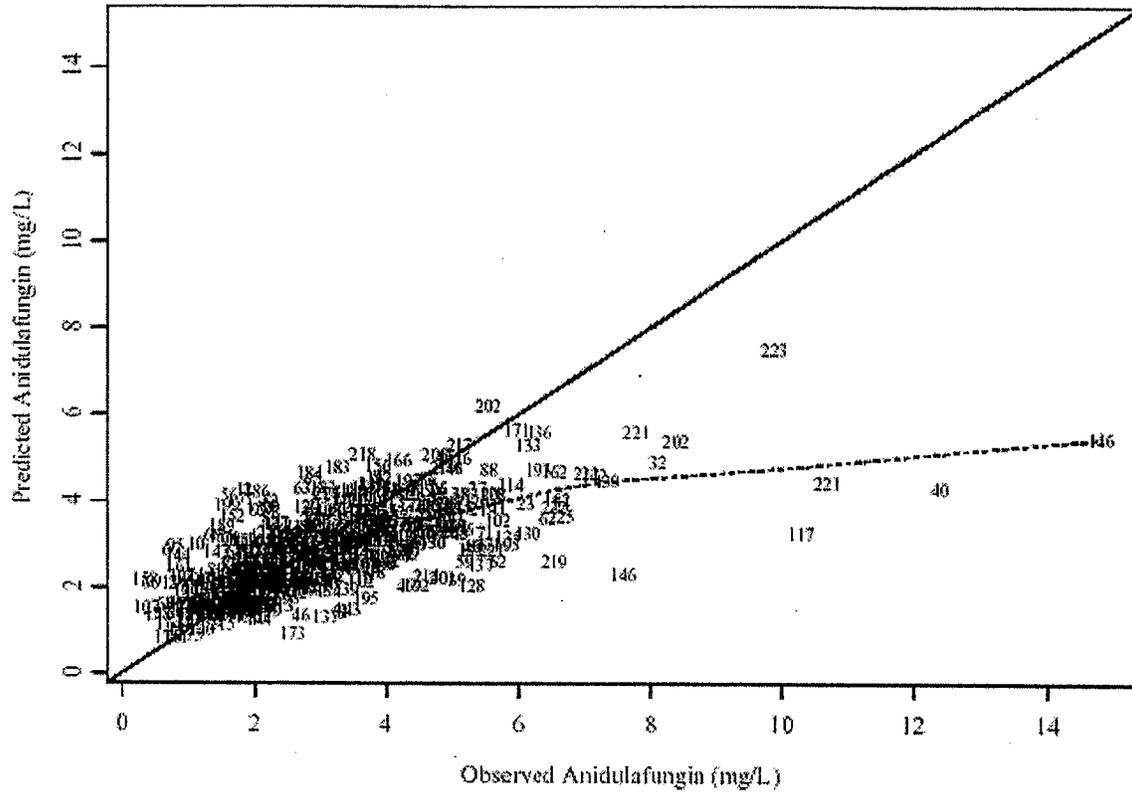
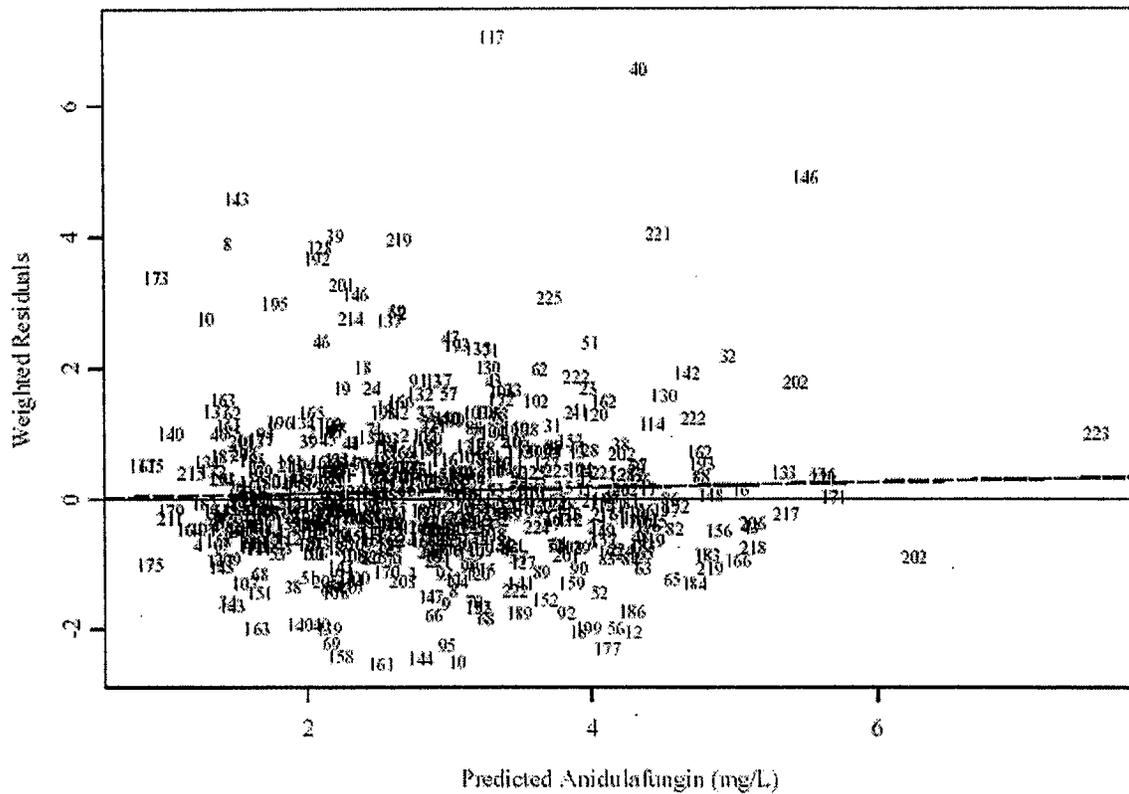


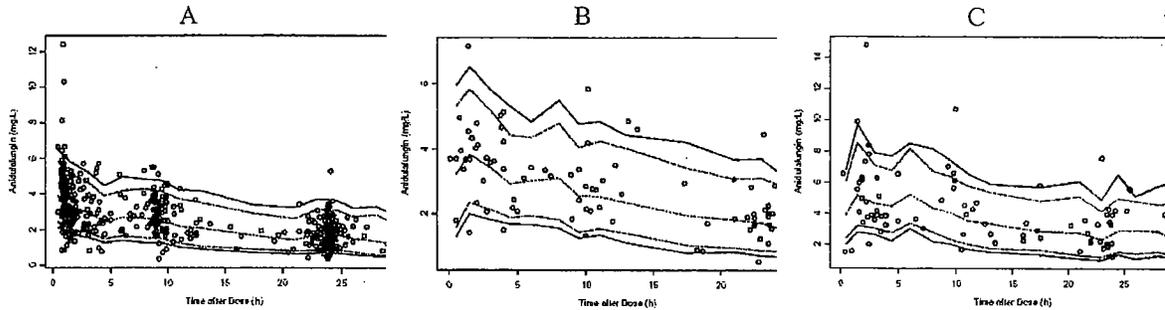
Figure 3: Weighted Residuals vs Predicted Anidulafungin Plasma Concentrations (Final Model)
 Weighted residuals versus final model (FOCEI method) population mean predicted Anidulafungin plasma concentrations are indicated by individual ID numbers and a LOESS smooth of the data (dotted line). A line at $y = 0$ (solid) is included as a reference.



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Figure 4: Model Evaluation of Anidulafungin Final Population Pharmacokinetic Model for the 100 mg/50 mg Dose Group (A), the 150 mg/75 mg Dose Group (B), and for the 200 mg/100 mg Dose Group (C)

Data points are the observed Anidulafungin plasma concentration vs time data.
Solid line represents the median; long dashed lines represent the 10th (lower) and 90th (upper) percentiles of the simulated Anidulafungin plasma concentrations vs. time data; short dashed lines represent the 20th and 80th percentiles of the simulated Anidulafungin plasma concentrations vs. time data.



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Appendix C. Cover Sheet and OCPB Filing/Review Form

| Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form | | | | |
|---|---------------------------|-----------------------------|---|--|
| General Information About the Submission | | | | |
| | Information | | Information | |
| NDA Number | 21-632 | Brand Name | N/A | |
| OCPB Division (I, II, III) | III | Generic Name | Anidulafungin | |
| Medical Division | DSPIDP | Drug Class | Antifungal | |
| OCPB Reviewer | Dakshina M. Chilukuri | Indication(s) | Esophageal candidiasis | |
| OCPB Team Leader | Philip Colangelo | Dosage Form | IV infusion | |
| | | Dosing Regimen | 100 mg loading dose on day-1 followed by 50 mg qd maintenance dose for 14-21 days | |
| Date of Submission | 4/25/03 | Route of Administration | Intravenous | |
| Estimated Due Date of OCPB Review | 12/24/03 | Sponsor | Vicuron Pharmaceuticals Inc. | |
| PDUFA Due Date | 2/24/04 | Priority Classification | Normal | |
| Division Due Date | 1/24/04 | | | |
| Clin. Pharm. and Biopharm. Information | | | | |
| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
| STUDY TYPE | | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | x | | | |
| Tabular Listing of All Human Studies | x | | | |
| HPK Summary | x | | | |
| Labeling | x | | | |
| Reference Bioanalytical and Analytical Methods | x | | | |
| I. Clinical Pharmacology | | | | |
| Mass balance: | x | 1 | | |
| Isozyme characterization: | x | 1 | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | x | 1 | | |
| Pharmacokinetics (e.g., Phase I) - <i>Healthy Volunteers-</i> | | | | |
| single dose: | x | 2 | | |
| multiple dose: | x | 4 | | |
| <i>Patients-</i> | | | | |
| single dose: | | | | |
| multiple dose: | x | 8 | | Sponsor has submitted PK data in patients from studies performed to evaluate the efficacy of anidulafungin in a variety of indications. PK data from 4 of these studies was used to perform Population PK analysis |
| Dose proportionality - | | | | |
| fasting / non-fasting single dose: | x | 1 | | |
| fasting / non-fasting multiple dose: | | | | |
| Drug-drug interaction studies - | | | | |
| In-vivo effects on primary drug: | x | 1 | | Drug-Interaction study with cyclosporine |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | x | 3 | | |
| Subpopulation studies - | | | | |
| ethnicity: | | | | |
| gender: | | | | |

| | | | | |
|---|--|-----------------|--|--|
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | x | 1 | | |
| hepatic impairment: | x | 1 | | |
| PD: | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| PK/PD: | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| Population Analyses - | | | | |
| Data rich: | | | | |
| Data sparse: | x | 4 | | Data from 4 studies were included in one population PK analysis |
| II. Biopharmaceutics | | | | |
| Absolute bioavailability: | x | 1 | | The applicant has submitted data from three studies performed to ascertain the oral bioavailability of anidulafungin |
| Relative bioavailability - | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | x | 1 | | |
| Bioequivalence studies - | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| Food-drug interaction studies: | | | | |
| Dissolution: | | | | |
| (IVVC): | | | | |
| Bio-wavier request based on BCS | | | | |
| BCS class | | | | |
| III. Other CPB Studies | | | | |
| Genotype/phenotype studies: | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | | | | |
| Filability and QBR comments | | | | |
| | "X" if yes | <u>Comments</u> | | |
| Application filable ? | X | | | |
| Comments sent to firm ? | | None | | |
| QBR questions (key issues to be considered) | Is the sponsor's conclusion regarding absence of any significant drug interactions with anidulafungin acceptable | | | |
| Other comments or information not included above | A pharmacometrics consult form will be submitted to request a review of the population pharmacokinetic analyses performed by the applicant in support of the NDA | | | |
| Primary reviewer Signature and Date | | | | |
| Secondary reviewer Signature and Date | | | | |

CC: NDA 21-632, HFD-850(P. Lee), HFD-880 (J. Lazor), HFD-590(CSO), CDR

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Dakshina Chilukuri
5/14/04 09:32:59 AM
BIOPHARMACEUTICS

Phil Colangelo
5/14/04 11:04:48 AM
BIOPHARMACEUTICS