# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-003**

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

# EXCLUSIVITY SUMMARY

NDA # 22-003 SUPPL # N/A HFD # 590

Trade Name Noxafil

Generic Name posaconazole

Applicant Name Schering Corporation

Approval Date, If Known June 22, 2006

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

## PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 ! <br> !

IND # YES ☐ ! NO ☐ <br> ! Explain:

Investigation #2 ! <br> !

IND # YES ☐ ! NO ☐ <br> ! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

| | |
|---|---|
| Investigation #1 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |

| | |
|---|---|
| Investigation #2 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Kristen Miller, Pharm.D.
Title: Regulatory Health Project Manager
Date: May 30, 2006

Name of Office/Division Director signing form: Renata Albrecht, M.D.
Title: Director, Division of Special Pathogen and Transplant Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

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Renata Albrecht
5/31/2006 02:14:13 PM

# PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

**NDA:** 22-003 **Supplement Type (e.g. SE5):** N/A **Supplement Number:**

**Stamp Date:** December 22, 2005 **Action Date:** June 22, 2006

**HFD-**590 **Trade and generic names/dosage form:** Noxafil (posaconazole) Oral Suspension

**Applicant:** Schering Corporation **Therapeutic Class:** Systemic Antifungal (7030410)

**Indication(s) previously approved:** None

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

**Number of indications for this application:** 1

**Indications:**
Prophylaxis of invasive fungal infections

**Is there a full waiver for this indication (check one)?**

- ☐ **Yes: Please proceed to Section A.**

- X **No: Please check all that apply:** ____**Partial Waiver** __X__**Deferred** __X__**Completed**
  **NOTE: More than one may apply**
  **Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

## Section A: Fully Waived Studies

**Reason(s) for full waiver:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section B: Partially Waived Studies

**Age/weight range being partially waived:**

| | | | | |
|---|---|---|---|---|
| **Min**_____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |
| **Max**_____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |

**Reason(s) for partial waiver:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section C: Deferred Studies

**Age/weight range being deferred:**

| | | | | |
|---|---|---|---|---|
| **Min** _____ | **kg**_____ | **mo.**_____ | **yr.** 0 | **Tanner Stage**_____ |
| **Max**_____ | **kg**_____ | **mo.**_____ | **yr.** 12 | **Tanner Stage**_____ |

**Reason(s) for deferral:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- **X Adult studies ready for approval**
- ☐ **Formulation needed**

**Other:**_____

**Date studies are due (mm/dd/yy):** 6/22/2011

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section D: Completed Studies

**Age/weight range of completed studies:**

| | | | | |
|---|---|---|---|---|
| **Min** _____ | **kg**_____ | **mo.**_____ | **yr.** 13 | **Tanner Stage**_____ |
| **Max**_____ | **kg**_____ | **mo.**_____ | **yr.** 17 | **Tanner Stage**_____ |

**Comments: Studies for the prophylaxis indication included patients down to 13 years of age.**

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**This page was completed by:**

*{See appended electronic signature page}*

*Kristen Miller, Pharm.D.*
**Regulatory Project Manager**

**cc: NDA 22-003 and HFD-960/ Grace Carmouze**
**(revised 12-22-03)**
FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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/s/

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Kristen Miller
5/30/2006 08:24:10 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

# Teleconference Minutes

**Teleconference Date:** June 22, 2006
**Application Numbers:** NDA 22-003
Noxafil (posaconazole) Oral Suspension
**Sponsor:** Schering Corporation
**Attendees:**

**Schering Corporation**

| | |
|---|---|
| Catherine Hardalo, MD | Senior Director, Anti-Infective Global Clinical Development (GCD) |
| Rob Kowalski, Pharm.D. | Vice President, Global Regulatory Affairs (GRA) |
| Penelope Giles, Ph.D. | Senior Director, Anti-Infectives, GRA |
| Todd Paporello, PharmD, MBA | Associate Director & Liaison, GRA |

**Office of Antimicrobial Products (OAP)**

| | |
|---|---|
| Edward Cox, M.D. | Deputy Director, OAP |
| Renata Albrecht, M.D. | Director, Division of Special Pathogen and Transplant Products (DSPTP) |
| Leonard Sacks, M.D. | Medical Team Leader, DSPTP |
| Maureen Tierney, M.D. | Medical Reviewer, DSPTP |
| Diana Willard | Chief, Project Management Staff, DSPTP |
| Kristen Miller, Pharm.D. | Regulatory Project Manager, DSPTP |

**BACKGROUND:** On December 21, 2005, Schering Corporation (Schering) submitted a new NDA (NDA 22-003) for Noxafil (posaconazole) Oral Suspension. This application was split for our administrative purposes and assigned a second NDA number, 22-027. NDA 22-003 was granted a priority review for the indication of prophylaxis of invasive fungal infections and NDA 22-027 was granted a standard review for the indication of treatment of oropharyngeal candidiasis. The action date for NDA 22-003 is June 22, 2006. On June 22, 2006, OAP called Schering to inform them that an action would not be taken that day.

**DISCUSSION POINTS:**

Schering was told that the Review Team had been working conscientiously to finalize the reviews of posaconazole for the indication of prophylaxis of invasive fungal infections; however, given the complexity of the application and numerous issues emerging during final negotiations on the label, more time was needed to integrate the information in a responsible fashion before taking an action on this new molecular entity. OAP would therefore be missing the June 22, 2006 goal date.

Schering asked what specifically was missing to hold up the action. OAP indicated that more time was needed to review the entire package before a final regulatory decision could be taken.

Schering asked if OAP has any reason to believe that the action would be different from the expected regulatory action. The Office noted that there was not enough time to complete the review, but this was not because of any adverse findings; therefore, a change in the nature of the action is not anticipated.

Schering asked for an estimate of when the action might occur. If no outstanding issues needed to be addressed, OAP hoped to take an action in the next few weeks; however, an action was not anticipated within a week.

Schering stated their disappointment but understood the time constraints. OAP recognized the dedication and hard work put into this application by both Schering and the Division and Office, but stressed that more time was needed to digest all of the information. DSPTP would be in contact with Schering in the next week to provide an update on the progression and a more firm time estimate. Recognizing the teams' hard work, Schering offered to provide the Review Team any analyses/information needed, and expressed a strong desire to have posaconazole on the market as soon as possible.

**Minutes Preparer:** Kristen Miller, Pharm.D., Regulatory Health Project Manager
**Chair Concurrence:** Ed Cox, M.D., Acting Director

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/s/
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Kristen Miller
9/15/2006 01:38:12 PM
CSO

Edward Cox
9/15/2006 01:59:25 PM
MEDICAL OFFICER

We appreciate the cooperation shown Investigator Koller during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

*{See appended electronic signature page}*

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

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/s/

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Leslie Ball
9/15/2006 04:03:57 PM

6 Page(s) Withheld

6 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-_____*

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

**Date:** September 6, 2006
**To:** NDAs 22-003/ Schering Corporation
**From:** Kristen Miller, Pharm.D.
**Subject:** Use of data from [redacted] sites

On December 21, 2005, Schering submitted NDA 22-003 for Noxafil® (posaconazole) Oral Suspension, 200mg/5mL. NDA 22-003 was granted a priority review for the indication of prophylaxis of invasive fungal infections. Protocol C98-316, entitled "Phase III Randomized, Double-Blind (Double Dummy) Study of the Safety, Tolerance and Efficacy of SCH 56592 vs. Fluconazole in the Prophylaxis of Invasive Fungal Infections in High Risk Recipients of Allogenic Progenitor Cell Transplantation with Graft-Versus-Host Disease" was a submitted to support this indication.

Between March 10, 2006 and April 6, 2006, a directed clinical inspection of a clinical investigator, [redacted] was conducted in response to a complaint received from the [redacted]
The complaint alleged noncompliance with protocols for two oncology studies, and noncompliance with drug accountability, drug administration, data collection, data documentation and toxicity reporting as well as problems with IRB submissions for protocol C98-316. A Form FDA 483 was issued, a final recommendation of OAI was made, and a Warning Letter will be issued to [redacted].

On August 8, 2006, the Division was notified that DSI considers the data not reliable from [redacted] site for the audited studies. DSI stated that it is up to the review division to decide whether to accept DSI's recommendation that the data be excluded from consideration in NDAs.

On August 18, 2006, Schering Plough was notified that the Division will exclude [redacted] data from both the safety and efficacy analyses. On August 29, 2006, Schering submitted response documents in defense of retaining [redacted] data in their analysis for C98-316. DSI is reviewing these documents and will provide a recommendation to the Division.

**MEMORANDUM**

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/s/
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Kristen Miller
9/6/2006 08:58:38 AM
CSO

Leslie Ball
9/7/2006 11:11:43 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-003

Schering Corporation
Attention: Todd Paporello, Pharm.D.
Regulatory Affairs Manager, Global Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Paporello:

On August 21, 2006, this office sent you the following document: the 483 issued for [redacted]. FDA requires further review of the information for releasability. We will send you another redacted copy of the record when we conclude our review.

In our telephone conversation on August 31, 2006, you agreed to return the original document and any copies that you made. You further agreed not to retain any copies of the documents or to use, distribute, or disclose the document or the contents thereof. Please confirm this agreement in a letter.

The letter, along with the document and any copies, should be sent to my attention at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Transplant Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

We apologize for the inadvertent disclosure of information to you. If you have questions, please call me at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Kristen Miller, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

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Kristen Miller
8/31/2006 01:32:23 PM

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** June 6, 2006
**APPLICATION:** NDA 22-003
NDA 22-027
**DRUG NAME:** Noxafil® (posaconazole) Oral Suspension
**TYPE OF MEETING:** Pre-Approval Safety Conference

**ATTENDEES:**

Mark Goldberger, M.D., MPH, Director [Office of Antimicrobial Products (OAP)]
David Roeder, M.S., Associate Director, Regulatory Affairs (OAP)
Renata Albrecht, M.D. Division Director [Division of Special Pathogen and Transplant Products (DSPTP)]
Rosemary Johann-Liang, M.D. Deputy Director [Office of Surveillance and Epidemiology (OSE)/Division of Drug Risk Evaluation (DDRE)]
Melissa Truffa, R.Ph., Safety Evaluator Team Leader (OSE/DDRE)
Jenna Lyndly, Pharm.D., Project Manager (OSE/DDRE)
Todd Bridges, Pharm.D., Safety Evaluator, [OSE/Division of Medication Errors and Technical Support (DMETS)]
Sammie Beam, Pharm.D. Regulatory Health Project Manager (OSE/DDRE)
Leonard Sacks, M.D. Medical Team Leader (DSPTP)
Maureen Tierney, M.D., Medical Reviewer (DSPTP)
Regina Alivisatos, M.D., Medical Reviewer (DSPTP)
Karen Higgins, Sc.D., Statistics Team Leader (Division of Biometrics III)
Cheryl Dixon, Ph.D., Statistics Reviewer (Division of Biometrics IV)
Jyoti Zalkikar, Ph.D., Statistics Reviewer (Division of Biometrics IV)
William Taylor, Ph.D. Pharmacology Toxicology Team Leader (DSPTP)
Owen McMaster, Ph.D. Pharmacology Toxicology Reviewer (DSPTP)
Mark Seggel, Ph.D. Chemistry Reviewer (Office of New Drug Quality Assessment)
Philip Colangelo, Ph.D. Clinical Pharmacology Team Leader (OCP/DCP4)
Seong Jang, Ph.D. Clinical Pharmacology Reviewer (OCP/DCP4)
Kalavati Suvarna, Ph.D., Microbiology Reviewer (DSPTP)
Shukal Bala, Ph.D., Microbiology Team Leader (DSPTP)
Kristen Miller, Pharm.D., Regulatory Project Manager (DSPTP)

**MEETING OBJECTIVES:**

The purpose of the PSC is to:

- Ensure the Office of Surveillance and Epidemiology's (OSE) Division of Drug Risk Evaluation (DDRE) is aware of potential postmarketing safety problems with posaconazole.
- Consider the need for any special postmarketing analyses/safety studies or evaluations to be agreed to by Schering prior to approval.
- Determine if there is any specific information or feedback that the Division would like from OSE.

**BACKGROUND:**

On December 21, 2005, Schering submitted NDA 22-003 for Noxafil® (posaconazole) Oral Suspension, 200mg/5mL. This application was split for our administrative purposes and assigned a second NDA number, 22-027. NDA 22-003 was granted a priority review for the indication of prophylaxis of invasive fungal infections, and NDA 22-027 was granted a standard review for the indication of treatment of oropharyngeal candidiasis. On June 22, 2006, NDA 22-003 will be approved for the indication of prophylaxis of invasive *Aspergillus* and *Candida* infections.

**DISCUSSION POINTS:**

Following introductions, a summary of the posaconazole safety for the prophylaxis of invasive fungal infections (IFI) was provided. Posaconazole is a relatively well tolerated azole with some of the same safety concerns as other members of the azole class and some possibly unique safety issues. The following potential safety concerns were discussed:

**Hepatic Effects**
The Division noted that an increase in hepatic adverse events including elevation in liver function tests and rare cases of severe liver injury have been seen in patients with severe underlying co-morbidity. Including this in the WARNING or PRECAUTION section of the labeling is recommended. DDRE noted that if posaconazole will be used in an outpatient setting, monitoring of liver function tests during the course of posaconazole therapy may be difficult; however, these patients may be less at risk as patients may not have as severe co-morbidities.

**Drug Interactions**
Posaconazole is an inhibitor of CYP3A4. Drug interactions have been noted with posaconazole and cyclosporine which can lead to severe, even fatal, cyclosporine toxicity (one death in the prophylaxis study). Additionally, interactions have been seen with tacrolimus. The Review Team plans to include the cyclosporine interaction and potentially fatal toxicity information in the WARNINGS section. DDRE asked if other azoles have similar interactions and if posaconazole would be the only label to contain wording regarding the fatalities with cyclosporine. The Review Team agreed that this may be the only product with such wording, and verified that other azoles have similar interactions with cyclosporine.

> **Addendum:** The Review Team consulted OSE to review the AERS database for any serious and/or fatal drug interactions in patients taking other azoles concomitantly with cyclosporine, tacrolimus, or sirolimus.

**Cardiotoxicity**
A thorough QT study was conducted and patients receiving prophylaxis with posaconazole and fluconazole had similar rates of increase of >60msec of QTc from baseline and QTc over 500 msec. Similar events were not recorded in healthy subjects receiving posaconazole. There was one case of torsades de pointes in patients with severe electrolyte abnormalities receiving prophylaxis with posaconazole. Additionally, a mild increase in incidence of significant hypokalemia (13%) was seen in patients receiving posaconazole compared to patients receiving fluconazole (10%). These events will be included in the PRECAUTIONS section of the labeling.

**Pulmonary Embolus**
There was an increase in the number of patients with pulmonary emboli in the post stem cell transplant patients with graft versus host disease (GVHD) who received posaconazole in comparison to fluconazole (6 patients versus 0 patients). These events will be included in the ADVERSE REACTIONS section of the labeling. A post-marketing commitment may also be added to monitor the incidence of pulmonary emboli.

**Blood Dyscrasias**
Mild increases in hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) (and overall thrombocytopenia) were seen in the post stem cell transplant patients with GVHD who received posaconazole in comparison to fluconazole. These events will be included in the ADVERSE REACTIONS section of the labeling. A post-marketing commitment may also be added to monitor the incidence of TTP and HUS.

**Neurophospholipidosis**
DDRE asked for an update on neurophospholipidosis seen in animal studies. The Review Team stated that phospholipidosis has been seen in fluconazole and itraconazole, but that neurophospholipidosis has only been found in studies with posaconazole. Neurophospholipidosis was seen after approximately three months of posaconazole dosing in dogs, but no changes were seen in functional testing. Additionally, no neurophospholipidosis or functional changes were seen in monkeys or human studies. DDRE asked if specific imaging or clinical neurotoxicity assessments were systematically performed in human studies. The Review Team stated that although specific monitoring was not performed in any human studies to date, there were no differences in the incidence of neurological adverse events between posaconazole and comparator arms of the human studies. DDRE stated that neurotoxicity will need to be closely monitored after posaconazole is on the market.

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Mark Goldberger
8/8/2006 09:52:20 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

# Teleconference Minutes

**Teleconference Date:** June 21, 2006
**Application Numbers:** NDA 22-003
Noxafil (posaconazole) Oral Suspension
**Sponsor:** Schering Corporation
**Attendees:**

**Schering Corporation**

| | |
|---|---|
| Ronald Garutti, MD | Group Vice President, Global Regulatory Affairs (GRA) |
| Catherine Hardalo, MD | Senior Director, Anti-Infective Global Clinical Development (GCD) |
| Hernando Patino, MD | Director, Anti-Infective GCD |
| Gopal Krishna, PhD | Associate Director, Drug Metabolism & Pharmacokinetics (DMPK) |
| Angela Sansone-Parsons, PharmD | Associate Director, ECREM |
| Gene Wright, PharmD, PhD | Executive Director, Global Project Management |
| Sharon Olmstead | Vice President, GRA |
| Todd Paporello, PharmD, MBA | Associate Director & Liaison, GRA |
| Andy Parratt | Marketing Director, Global Pharmaceutical Business |
| Polina Fradkin | Senior Manager, GRA Global Labeling |
| Lori Lucas, PhD | Director, GRA Global Promotion |
| Ram Suresh, PhD | Director, Statistics |

**Division of Special Pathogen and Transplant Products (DSPTP)**

| | |
|---|---|
| Renata Albrecht, M.D. | Director |
| Leonard Sacks, M.D. | Medical Team Leader |
| Maureen Tierney, M.D. | Medical Reviewer |
| Regina Alivisatos, M.D. | Medical Reviewer |
| Kristen Miller, Pharm.D. | Regulatory Project Manager |

**BACKGROUND:** On December 21, 2005, Schering submitted a new NDA for Noxafil (posaconazole) Oral Suspension. On June 20, 2006, Schering Plough sent proposed wording for a post-marketing commitment to study different dosing strategies to increase posaconazole's plasma concentration. During previously scheduled June 21, 2006 teleconference, the Review Team and Schering further discussed the post-marketing commitments for posaconazole.

**DISCUSSION POINTS:**

Schering's June 20, 2006 post-marketing commitment proposal was to conduct a study in patients receiving antifungal prophylaxis. They clarified that while the Division would prefer the study be done in patients receiving posaconazole for treatment, physicians will not use an oral medication for first line treatment of *Aspergillus*. The Division acknowledged this and agreed to the proposed wording with the addition of the phrase "including the use of therapeutic drug monitoring". Schering agreed with this inclusion; the agreed to commitment is "A post approval study will be conducted among patients receiving antifungal prophylaxis. The study will enroll patients who are at risk for low absorption. Different dosing strategies including the use of therapeutic drug monitoring to increase plasma concentrations will be explored." Schering proposed to submit the protocol by October 2006, initiate the study within six months of FDA/Schering agreement on the study design, and submit the final report by December 2010; however, the Division noted that specific dates must be included for tracking purposes and proposed that the study start by October 2007. Schering agreed.

The Division requested the following two additional post-marketing commitments:

1. Detailed reports of thrombotic or microangiopathic events, such as hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), pulmonary embolus, etc. will be submitted quarterly for three years.

2. Utilization data and indications, when known, will be submitted every six months for three years.

Schering agreed to these commitments and will submit a letter to the Division on June 22, 2006.

**ADDENDUM**: Schering submitted a letter agreeing to these commitments on June 22, 2006.

**Minutes Preparer:** Kristen Miller, Pharm.D., Regulatory Health Project Manager
**Chair Concurrence:** Renata Albrecht, M.D., Director

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/s/
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Kristen Miller
7/13/2006 04:23:46 PM
CSO

Renata Albrecht
7/17/2006 05:17:24 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

# Teleconference Minutes

**Teleconference Date:** May 26, 2006
**Application Numbers:** NDAs 22-003 and 22-027
Noxafil (posaconazole) Oral Suspension
**Sponsor:** Schering Corporation
**Attendees:**

**Schering Corporation**

| | |
|---|---|
| Ronald Garutti, MD | Group Vice President, Global Regulatory Affairs (GRA) |
| Penny Giles, PhD | Senior Director, Global Regulatory Affairs |
| Catherine Hardalo, MD | Senior Director, Anti-Infective Global Clinical Development (GCD) |
| Hernando Patino, MD | Director, Anti-Infective GCD |
| Gopal Krishna, PhD | Associate Director, Drug Metabolism & Pharmacokinetics (DMPK) |
| Pratapa Prasad, PhD | Senior Director, DMPK |
| Allen Moton, PharmD | Associate Director, Early Clinical Research (ECREM) |
| Angela Sansone-Parsons, PharmD | Associate Director, ECREM |
| Gene Wright, PharmD, PhD | Executive Director, Global Project Management |
| Sharon Olmstead | Vice President, GRA |
| Todd Paporello, PharmD, MBA | Associate Director & Liaison, GRA |

**Division of Special Pathogen and Transplant Products**

| | |
|---|---|
| Renata Albrecht, M.D. | Director |
| Philip Colangelo, Pharm.D., Ph.D. | Clinical Pharmacology Team Leader |
| Seong Jang, Ph.D | Clinical Pharmacology Reviewer |
| Jogarao Gobburu, Ph.D. | Pharmacometrics Team Leader |
| Leonard Sacks, M.D. | Medical Team Leader |
| Maureen Tierney, M.D. | Medical Officer Reviewer |
| Karen Higgins, Sc.D. | Statistics Team Leader |
| Jyoti Zalkikar, Ph.D. | Statistics Reviewer |
| Kristen Miller, Pharm.D. | Regulatory Project Manager |

**BACKGROUND:** On December 21, 2005, Schering submitted a new NDA for Noxafil (posaconazole) Oral Suspension. On May 23, 2006, Schering was informed that in the process of completing their review, the Review Team's clinical pharmacologists determined that there is a impressive difference in the clinical outcome and incidence of proven/probable IFI in the lowest quartile of patients (based on posaconazole levels) as opposed to the three higher quartiles of posaconazole patients or to the comparator in Study 98-316. Questions were sent along with a request for this teleconference in order to discuss this finding. On May 25, 2006, Schering submitted a response to the May 23, 2006 questions in preparation for this teleconference.

**DISCUSSION POINTS:**

Following introductions, the Division thanked Schering for the quick response to the May 23, 2006 questions, but stated that the response was just received so the Division could not comment on it. Schering then quickly summarized what was submitted. Regarding Schering's May 25, 2006 submission, the Division had asked if the exposure-response relationship is confounded by any other factors (for example food intake, disease severity, treatment period, baseline factors, etc.). Schering was asked to identify patients with similar confounding risk factors on fluconazole so that they can be compared to the posaconazole group to determine if the two groups are similar. Schering conducted an analysis that took into account three risk factors for being in the low concentration group, gender, CMV status, and acute or chronic GVHD. The Review Team was concerned that these three risk factors alone would not provide an adequate prediction of which patient would obtain low concentration and asked Schering to include additional important risk factors in the model. Schering noted that they believed that all clinically relevant factors had been included and asked the Division to provide additional specific risk factors they would like to see included. The Review Team will provide these to Schering by May 30, 2006. Schering also noted that a much higher proportion of patients in the lowest quartile (Q1) had samples collected more than two days after the last dose compared with patients in the highest quartile (Q4). The Division requested a new analysis excluding all samples which were collected more than twenty-four hours after the last dose. Schering agreed.

Through the course of the review, the Division has noticed variability in posaconazole exposure. Optimal response to therapy is unlikely with limited exposure; therefore, the Division would like to get a sense of what population does not absorb posaconazole to provide appropriate labeling to optimize therapy. Schering was asked to provide a rationale for why the lack of absorption in the lowest quartile of posaconazole dosed patients should not cause concern.

Schering agreed to provide a table showing the time relationship between death and the end of therapy for Q1 and Q4. The table should be similar to Table 2 provided by Schering on May 25, 2006, replacing IFI onset with death.

**ACTION ITEMS**

1. The Review Team will provide additional specific risk factors to be included from the analysis to Schering by May 30, 2006.
2. Schering will submit a new analysis excluding patients that had samples collected more than twenty-four hours after the last dose of posaconazole.
3. Schering will provide a table showing the time relationship between death and the end of therapy for Q1 and Q4.
4. Schering was asked to provide a rationale for why the Review Team should not be concerned about the lack of absorption in the lowest quartile of posaconazole dosed patients.

**Minutes Preparer:** Kristen Miller, Pharm.D., Regulatory Health Project Manager
**Chair Concurrence:** Renata Albrecht, M.D., Director

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/s/
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Kristen Miller
6/26/2006 10:16:42 AM
CSO
For Renata Albrecht

Leonard Sacks
6/26/2006 03:15:39 PM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

# FACSIMILE TRANSMITTAL SHEET

**DATE:** June 14, 2006

| | |
|---|---|
| **To:** Todd Paporello, Pharm.D. | **From:** Kristen Miller, Pharm.D. |
| **Company:** Schering | Division of Special Pathogen and Transplant Products |
| **Fax Number:** 908-740-6500 | **Fax Number:** 301-796-9882 |
| **Phone Number**: 908-740-4252 | **Phone Number:** 301-796-0762 |

**Subject:** Comments and requests regarding NDAs 22-003

**Total no. of pages including cover:**

**Comments:** Concur:

| | |
|---|---|
| Maureen Tierney, M.D. | Medical Officer |
| Leonard Sacks, M.D. | Medical Team Leader |
| Jyoti Zalkikar, Ph.D. | Statistics Reviewer |
| Seong Jang, Ph.D. | Clinical Pharmacologist Reviewer |
| Philip Colangelo, PhD, PharmD | Clinical Pharmacologist Team Leader |

**Document to be mailed:** ☐ YES ☑ NO

NDA 22-003

Please refer to your new drug application (NDA) 22-003 for Noxafil® (posaconazole) Oral Suspension submitted on December 22, 2005. Please also refer to our teleconference scheduled for June 16, 2006. In preparation for this teleconference, the Review Team has the following comments:

As you are aware from our May 26, 2006 teleconference, we have determined from the data collected in studies C98-316 and P01899 that there was a very broad range of posaconazole concentrations achieved in patients who took the proposed dose of 200 mg po TID for the prophylaxis of invasive fungal infections (IFIs). The patient data, including posaconazole plasma concentrations, clinical outcomes and specifically the incidence of IFIs were carefully reviewed. Attached is a summary of all of these analyses which is more extensive than the summary supplied to you on May 26, 2006.

As you can see from these analyses, the data from these two clinical studies show a strong relationship between a higher incidence of clinical failure and lower plasma exposure to posaconazole. As mentioned in the June 5, 2006 facsimile, we continue to be concerned that the low success rates may be due, in part, to the corresponding low posaconazole plasma concentrations. Although other factors may also account for this finding, there is, for example, no convincing evidence that baseline risk factors alone can identify the patients who attained low plasma exposure to posaconazole.

The Review Team feels that although this finding does not preclude approval of posaconazole at this time, a better understanding of why certain patients achieve such low levels and how they should be managed is important to pursue. Consequently, during our June 16, 2006 teleconference, we would like to discuss with you how to further study this issue. Options could include a post-marketing study commitment to look at therapeutic drug monitoring using a scheme such as that outlined on page 6 of the attachment, or a drug/exposure response study in the treatment of certain invasive fungal infections, particularly *Aspergillus*.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-0762 if you have any questions.

_____

Kristen Miller, Pharm.D.
Regulatory Health Project Manager

**Summary of exposure-response analysis and potential dose recommendation based on the exposure-response relationship**

**Exposure-response relationship-Effectiveness**

The exposure-response analyses revealed a strong relationship between a higher incidence of Clinical Failure and lower plasma exposure to POS, suggesting that ensuring high plasma exposure to POS appears to be needed especially for patients whose steady state average concentration ($C_{avg}$) is low (See Figure 1). Table 1 shows the Clinical Failure rate and Proven/Probable IFIs in the All Treated population during the Primary Time Period for 4 quartiles of POS $C_{avg}$.

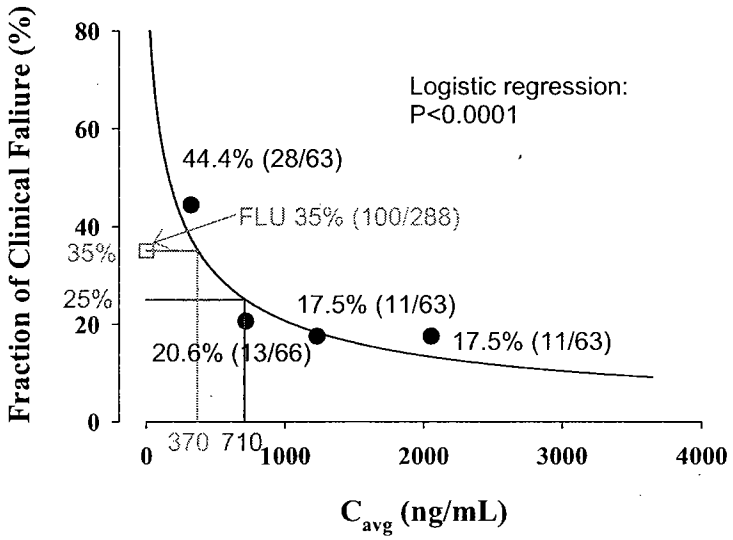



**Figure 1.** POS exposure-response relationship for patients in the All Treated population during the Primary Time Period (N=252) (Study C98-316). Logistic regression was performed using natural log of average concentrations per patient ($\log(C_{avg})$) as a continuous variable and the Clinical Failure as a binary variable (yes or no). The solid line represents the regression fit. Subsequent to the logistic regression, the response rates in each of the 4 quartiles of $C_{avg}$ (closed circles) are plotted to assess the goodness-of-fit. The response rate for patients treated with fluconazole (FLU, open square) is plotted as a reference. The blue lines showed that 710 ng/mL of $C_{avg}$ is required to achieve 25% Clinical Failure rate. The red lines showed that 370 ng/mL of $C_{avg}$ is required to achieve 35% Clinical Failure rate.

**Table 1.** Incidence of Clinical Failure in the All Treated population during the Primary Time Period in 4 quartiles of POS $C_{avg}$ (Study C98-316).

| Quartiles | Q1 | Q2 | Q3 | Q4 |
|---|---|---|---|---|
| **$C_{avg}$ (ng/mL)** | **21.5-557** | **557-915** | **915-1563** | **1563-3650** |
| **Clinical Failure** | **44.4% (28/63)** | **20.6% (13/63)** | **17.5% (11/63)** | **17.5% (11/63)** |
| Proven/probable IFI | 4.76% (3/63) | 4.76 % (3/63) | 1.59% (1/63) | 3.17% (2/63) |
| Empirical use of Sys. Antifungal [a] | 17.5% (11/63) | 3.17% (2/63) | 6.35% (4/63) | 4.76% (3/63) |
| Death | 34.9% (22/63) | 20.6% (13/63) | 17.5% (11/63) | 11.1% (7/63) |
| Discontinuation [b] | 23.8% (15/63) | 14.3% (9/63) | 9.52% (6/63) | 9.52% (6/63) |

There is some overlap in the rows.
[a]: Use of systemic antifungal agents in addition to study drug more than 5 days, from all causes
[b]: Discontinuation due to any reason

**Dose recommendation based on the exposure-response relationship**

There are no patient demographic covariates (or combination of those covariates) that can successfully identify the patients who will attain low plasma concentrations of POS. Therefore, measuring plasma concentrations of POS is considered by this reviewer to be the most reliable way to identify those patients who will attain low plasma concentrations of POS.

Based on the relationship between $C_{avg}$ of POS and Clinical Failure (See Figure 1), a Clinical Failure rate of <25% is considered to be acceptable by the reviewing medical officer as a target clinical outcome that should be achieved with POS and $C_{avg}$ should be greater than 700 ng/mL to achieve this target outcome. Thus, 700 ng/mL is the lower threshold value for $C_{avg}$ to determine if the POS dosage needs to be increased for a given patient. Subsequently, the concentration on Day 2 which would result in a $C_{avg}$ of 700 ng/ml at steady state was calculated using an accumulation factor of 8 obtained from a multiple dose-escalating PK study (Study I96089). Based on this, a concentration of 350 ng/mL measured at 3 to 5 hours post dose on Day 2 is recommended as a cutoff plasma concentration of POS to determine if the POS dosage needs to be increased for a given patient.

The threshold concentration of 700 ng/mL as $C_{avg}$ also appears appropriate in terms of the incidence of Proven/Probable IFIs, because the incidence of Proven/Probable IFIs also tended to be greater for patients whose $C_{avg}$ was ≤700 ng/mL compared with patients whose $C_{avg}$ was >700 ng/mL. Tables 2 and 3 shows the incidence of Prove/Probable IFIs between group of patients whose $C_{avg}$ was ≤700 ng/mL and group of patients whose $C_{avg}$ was >700 ng/mL in Study C98316 and P01899, respectively.

**Table 2.** Incidence of Proven/Probable IFIs between those patients whose POS $C_{avg}$ was ≤700 ng/mL and those patients whose POS $C_{avg}$ was >700 ng/mL (Study C98316).

| $C_{avg}$ (ng/mL) | ≤700 ng/mL (N=92) | >700 ng/mL (N=160) |
|---|---|---|
| Incidence of Prove/Probable IFIs | 6.52% (6/92) | 1.88% (3/160) |
| Incidence of Aspergillosis | 4.35% (4/92) | 0.63% (1/160) |

**Table 3.** Incidence of Proven/Probable IFIs between those patients whose $C_{avg}$ was ≤700 ng/mL and those patients whose $C_{avg}$ was >700 ng/mL (Study P01899).

| $C_{avg}$ (ng/mL) | ≤700 ng/mL (N=155) | >700 ng/mL (N=60) |
|---|---|---|
| Incidence of Prove/Probable IFIs | 3.87% (6/155) | 0% (0/60) |

Four clinical pharmacology studies (i.e., single and multiple dose escalating studies and food effect studies following 200 mg and 400 mg of POS) support that the increase of POS dose from 200 mg TID to 400 mg TID is most likely to result in an increase in plasma exposure to POS by at least 2 fold when POS is given either with food or under fasting conditions.

When dose is adjusted from 200 mg TID to 400 mg TID, based on the threshold $C_{avg}$ of 700 ng/mL, the percent of patients whose $C_{avg}$ is ≤700 ng/mL would be decreased from 37% (92/252) to 14% (35/252). The Clinical Failure rate for patients whose $C_{avg}$ was ≤700 ng/mL (i.e., with 200 mg TID) would be reduced from 37% (34/92) to 25% (23/92) (Table 4).

**Table 4.** Percent of patients whose $C_{avg}$ is ≤700 ng/mL and Clinical Failure rate as a function of POS dosing regimen

| $C_{avg}$ ≤700 ng/mL | 200 mg TID | 400 mg TID (projection) |
|---|---|---|
| % of patients whose $C_{avg}$ is ≤700 ng/mL | 37% (92/252) | 14% (35/252) |
| Clinical Failure rate in patients whose $C_{avg}$ was ≤700 ng/mL | 37% (34/92) | 25% (23/92) |

For patients whose plasma concentrations of POS cannot be high enough to ensure desirable clinical outcomes with 400 mg TID, other antifungal treatment for prophylaxis of IFIs may be needed. Thus, it is recommended to use other antifungal treatment instead of POS for patients who receive 400 mg TID and if plasma concentrations of POS after Day 7 (presumed steady state) are ≤700 ng/mL.

In summary, the exposure-response analysis showed:

(a) The exposure-response relationship for POS effectiveness for the prophylaxis against IFIs was not significantly confounded with any patient demographic covariates

(b) POS concentration of 350 ng/mL determined at 3 to 5 hours post dose on Day 2 after the beginning of POS treatment would result in a steady-state $C_{avg}$ of 700 ng/mL and subsequently result in the incidence of Clinical Failure of

<25%. Plasma concentration monitoring of POS may be used as a tool to identify those patients who will have lower than desired plasma exposure.

(c) The increase of POS dose from 200 mg TID to 400 mg TID is most likely to result in an increase in plasma exposure to POS by at least 2 fold when POS is given either with food or under fasting conditions.

Collectively, the following dose administration and plasma concentration monitoring scheme is recommended by this reviewer.

Initial dose: 200 mg TID for all patients

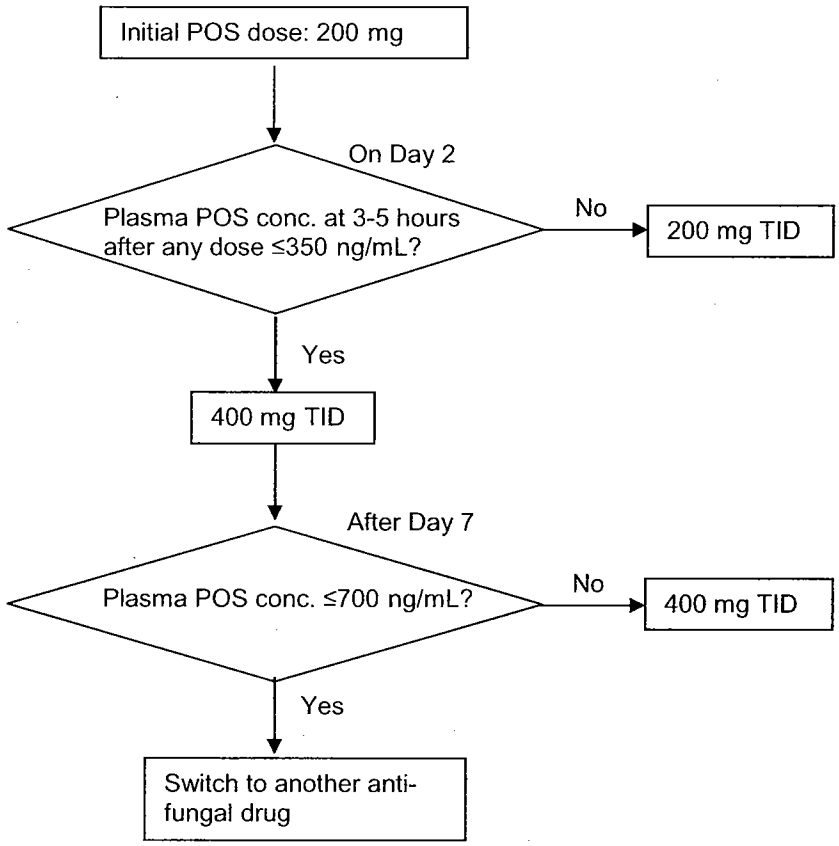
Monitoring of plasma concentration(s) of POS on Day 2:

Plasma samples should be collected at 3 to 5 hours after any dose on Day 2.

(a) If plasma concentration(s) of POS is ≤350 ng/mL, then give 400 mg TID
(b) If plasma concentration(s) of POS is >350 ng/mL, then give 200 mg TID

Monitoring of plasma concentration(s) of POS after Day 7 for patients who received 400 mg TID:

(a) If plasma concentration(s) of POS is >700 ng/mL, then give 400 mg TID
(b) If plasma concentration(s) of POS is ≤700 ng/mL, then switch to another anti-fungal drug




Scheme of POS Dose recommendation based on plasma concentrations of POS

**Exposure-response relationship-Safety**

The most common treatment-related (Possible and Probable) treatment-emergent adverse events were nausea, vomiting, diarrhea, hypokalemia, rash and elevations in hepatic enzymes (SGOT and SGPT increase). For exposure-response relationship regarding safety, data from Study C98316 and P01899 were pooled. Although the incidence of most treatment-related adverse events tended to be lower in the first quartile of $C_{avg}$ compared with the fourth quartile of $C_{avg}$, the incidence rates of adverse events were not significantly dependent on plasma drug concentration (Table 5).

**Table 5.** Incidence of treatment-emergent and drug-related (Possible and Probable) AEs (%) in the All Treated population in 4 quartiles of average plasma concentration POS ($C_{avg}$) (N=450; Studies C98-316 and P01988). Datasets from Study C98-316 and P01899 were pooled for these analyses.

| | 1st Q (n=119) | 2nd Q (N=121) | 3rd Q (N=120) | 4th Q (N=120) | P value[b] |
|---|---|---|---|---|---|
| $C_{avg}$ (ng/mL)[a] | 205±105 [2.51-355] | 498±77.1 [355-626] | 835±138 [626-1118] | 1751±538 [1118-3650] | |
| Diarrhea | 3.36% | 4.96% | 8.33% | 6.67% | 0.4378 |
| Nausea | 7.56% | 6.61% | 10% | 12.5% | 0.3746 |
| Vomiting | 3.36% | 4.96% | 7.5% | 6.67% | 0.4639 |
| Discontinuation | 8.4% | 7.44% | 14.2% | 17.5% | 0.0595 |
| Bilirubinemia | 1.68% | 3.31% | 4.17% | 3.33% | 0.4787 |
| SGOT increased | 1.68% | 2.48% | 4.17% | 3.33% | 0.4016 |
| SGPT increased | 1.68% | 3.31% | 5% | 3.33% | 0.4911 |
| Hepatic enz. increased | 1.68% | 3.31% | 4.17% | 3.33% | 0.4787 |
| Hypokalemia | 0.84% | 1.65% | 4.17% | 2.5% | 0.4818 |
| Rash | 0.84% | 1.65% | 4.17% | 3.33% | 0.1739 |

[a]: Mean±SD [range]

[b]: Logistic regression for the relationship between the incidence of treatment-related adverse events and $C_{avg}$

There would be expected to be no additional safety findings with 400 mg TID for those patients whose $C_{avg}$ was ≤700 ng/mL (i.e., those who receive 200 mg TID initially). Based on the dose-proportional PK of POS, following 400 mg TID administration to patients whose $C_{avg}$ was ≤700 ng/mL (i.e., those who receive 200 mg TID initially), $C_{avg}$ would not be expected to be greater than 3650 ng/mL, which is the highest $C_{avg}$ observed in patients treated with 200 mg TID in Study C98316.

## Appendix

**Table A1.** Incidence of Clinical Failure and Proven/Probable IFIs in the All Treated population during the Oral Treatment Phase in 4 concentration quartiles of POS (Study P01899).

| $C_{avg}$ (ng/mL) | Clinical Failure | Proven/probable IFI |
|---|---|---|
| 89.65-322 | 54.7% (29/53) | 3.77% (2/53) |
| 322-490 | 37.0% (20/54) | 1.85 % (1/54) |
| 490-733.5 | 46.3% (25/54) | 5.56% (3/54) |
| 733.5-2200 | 27.8% (15/54) | 0% (0/54) |

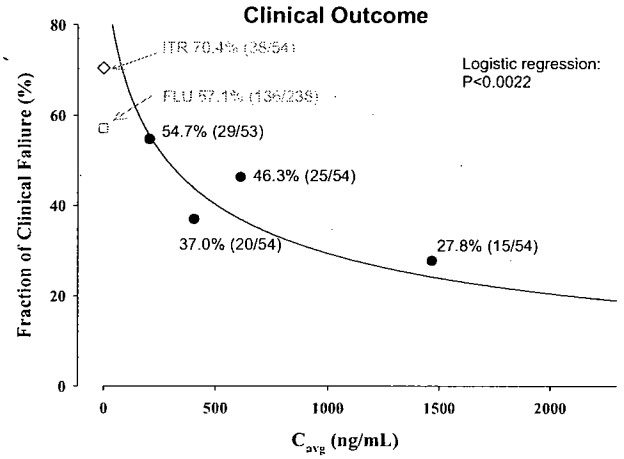



**Figure A1.** POS exposure-response relationship for patients in All Treated population during the Oral Treatment Phase (n=215) (Study P01899). Logistic regression was performed using natural log of average concentrations per patient ($\log(C_{avg})$) as a continuous variable and the Clinical Failure as a binary variable (yes or no). The solid line represents the regression fit. Subsequent to the logistic regression, the response rates in each of the 4 concentration quartiles (closed circles) are plotted to assess the goodness-of-fit. The response rates in patients treated with fluconazole (FLU, open square) and itraconazole (ITZ, open diamond) are plotted as references.

**Table A2.** Calculated plasma concentrations of POS before $C_{avg}$ reaches 700 ng/mL at Day 7 (presumed at steady state) following oral administration of POS 200 mg TID.

| Day | No. of Dose | Plasma concentration of POS (ng/mL) |
|---|---|---|
| 1 | 1 | 67 |
| | 2 | 186 |
| | 3 | 238 |
| 2 | 4 | 286 |
| | 5 | 331 |
| | 6 | 371 |
| 3 | 7 | 408 |
| | 8 | 442 |
| | 9 | 474 |
| 4 | 10 | 503 |
| | 11 | 529 |
| | 12 | 553 |
| 5 | 13 | 576 |
| | 14 | 596 |
| | 15 | 615 |
| 6 | 16 | 632 |
| | 17 | 648 |
| | 18 | 663 |
| 7 | 19 | 676 |
| | 20 | 689 |
| | 21 | 700 |

For the calculation, 7.6±2.8 of accumulation ratio ($R_{0\text{-}12h}$) obtained following oral administration of POS 200 mg BID for 14 days (Study I96089) were used.

**Table A3.** Pharmacokinetic parameters (Mean±SD [range]) of POS tablets on Day 14 after oral (Q12 hr) administration of POS tablets for 14 days (n=9/Dose) (Study I96-089)

| | 200 mg BID | 400 mg BID | Fold Difference |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 1753±466 [1020-2230] | 4150±816 [2920-5710] | 2.37 |
| $AUC_{0-12}$ (ng·hr/mL) | 16801±4319 [8929-21960] | 39206±8020 [24475-47985] | 2.33 |

**Table A4.** Pharmacokinetic parameters (Mean±SD [range]) of POS following single oral administration of POS tablets to healthy male volunteers (n=6 for each dose). (Study I95-098)

| | 200 mg | 400 mg | Fold Difference |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 332±70.8 [273-470] | 611±190 [424-964] | 1.84 |
| $AUC_{inf}$ (ng·hr/mL) | 10896±3411 [5650-14634] | 20264±6781 [12716-29387] | 1.86 |

**Table A5.** Pharmacokinetic parameters (Mean±SD [range]) of POS (n=20) after a single oral administration of 400 mg oral suspension after a 10-hr fast or a high-fat breakfast (Study I96099)

| | Suspension (fasted) | Suspension (high-fat meal) | Fold Difference |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 132±65.8 [45.7-267] | 512±176 [241-1016] | 3.88 |
| $AUC_{inf}$ (ng·hr/mL) | 4179±1285 [2705-7269] | 13885±5655 [7854-34824] | 3.3 |

**Table A6.** Pharmacokinetic parameters (Mean (CV%)) of POS (n=20) after a single oral administration of 200 mg oral capsule after a 10-hr fast or a high-fat breakfast (Study I95099)

| | Capsules (fasted) | Capsules (high-fat meal) | Fold Difference |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 102.3 (39%) | 531.4 (32%) | 5.2 |
| $AUC_{inf}$ (ng·hr/mL) | 3588 (37%) | 14293 (38%) | 3.98 |

**Table A7.** POS $C_{avg}$ in patients who has Proven/Probable IFIs (Study C98316)

| Subject ID | $C_{avg}$ (ng/mL) | Quartile | Pathogen |
|---|---|---|---|
| I004000048 | 99 | Q1 | Aspergillosis |
| I004000049 | 158 | Q1 | Aspergillosis |
| I004000050 | 319 | Q1 | Candidiasis |
| I004000051 | 565 | Q2 | Aspergillosis |
| I004000052 | 681 | Q2 | Aspergillosis |
| I004000053 | 691 | Q2 | Other Fungi |
| I004000054 | 1562 | Q3 | Aspergillosis |
| I004000055 | 2080 | Q4 | Candidiasis |
| I004000056 | 2190 | Q4 | Other fungi |

**Table A8.** POS $C_{avg}$ in patients who had Proven/Probable IFIs (Study P01899)

| Subject ID | $C_{avg}$ (ng/mL) | Quartile | Pathogen |
|---|---|---|---|
| 0054001468 | 254 | Q1 | Aspergillosis |
| 0010001371 | 294 | Q1 | Other Fungi |
| 0015001239 | 417 | Q2 | Aspergillosis |
| 0015001415 | 491 | Q3 | Candidiasis |
| 0057001492 | 606 | Q3 | Candidiasis |
| 0002001271 | 629 | Q3 | Other Fungi |

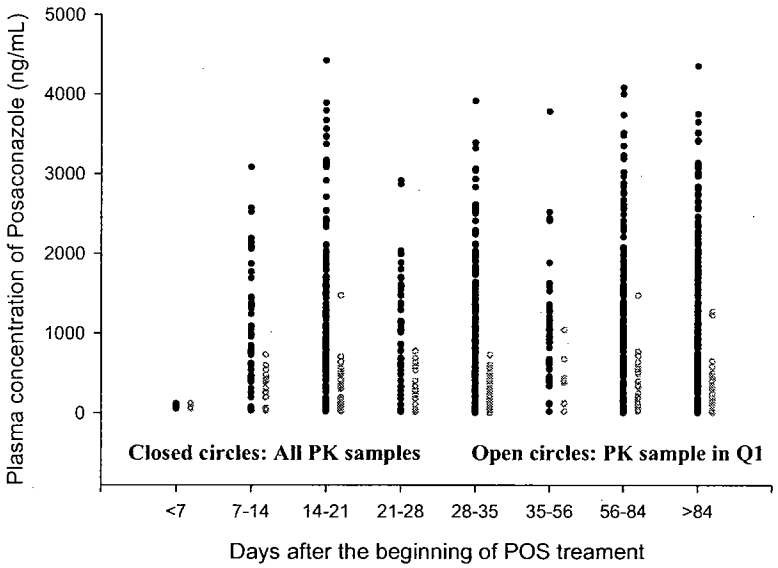



**Figure A2**. Plasma concentrations of POS (PK sample number=870) in all patients (n=252) as a function of time (days) after the beginning of POS treatment. (Study C98316)

**Effect of risk factors that the sponsor determined on exposure-response relationship of posaconazole**

A sub population (n=51) that the sponsor chose:

Acute GVHDBDID, male and CMV positive (A-M-C)

Based on new dataset (excluding plasma samples collected at more than 24 hr after last dose), 6 patients did not have $C_{avg}$ data and 46% of patients belong to Q1.

A sub population excluding this higher risk population (i.e., Not A-M-C; N=291-51=240):

Among this group, $C_{avg}$ values are available in 207 patients.

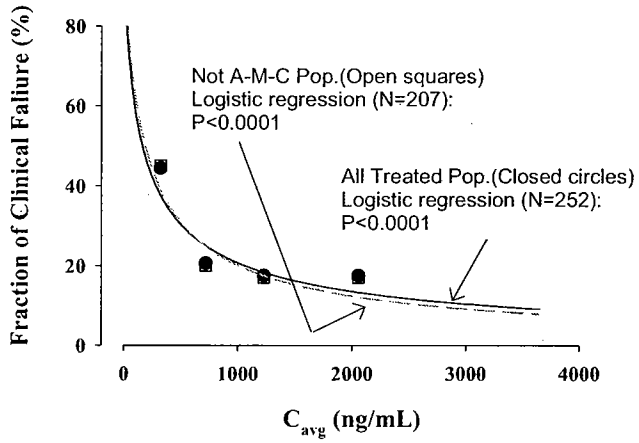
Clinical failure rate in 4 quartiles of $C_{avg}$ in A-M-C (N=45) vs. Not A-M-C (N=207)

| | Q1 (N=63) | Q2 (N=63) | Q3 (N=63) | Q4 (N=63) |
|---|---|---|---|---|
| A-M-C (N=45) | 43%(9/21) | 25% (3/12) | 22% (2/9) | 33% (1/3) |
| Not A-M-C (N=207) | 45% (19/42) | 20% (10/51) | 17% (9/54) | 17% (10/60) |
| Total (N=252) | 44.4% (28/63) | 20.6% (13/63) | 17.5% (11/63) | 17.5% (11/63) |

Clinical failure rate in Q1 vs. Q2-Q4 of $C_{avg}$ in A-M-C (N=45) vs. Not A-M-C (N=207)

| | Q1 (N=63) | Q2-Q4 (N=189) |
|---|---|---|
| A-M-C (N=45) | 43% (9/21) | 25% (6/24) |
| Not A-M-C (N=207) | 45% (19/42) | 18% (29/165) |
| Total (N=252) | 44.4% (28/63) | 19% (35/189) |

Logistic regression for Clinical Failure vs. $C_{avg}$ in this sub population



*Within a higher risk group, Clinical Failure rate was greater in Q1 compared with Q2-Q4, indicating that low plasma exposure to posaconazole is a major determinant for Clinical Outcome of posaconazole for the prophylaxis of IFIs (i.e., The exposure response relationship was not confounded with these risk factors)*

The same results obtained from another sub population (N=33).

Acute GVHDBDID, male, CMV positive and baseline Cort ≥ 1 (A-M-C-C)

Based on new dataset (excluding plasma samples collected at more than 24 hr after last dose), 6 patients did not have $C_{avg}$ data and 57% of patients belong to Q1.

A sub population excluding this higher risk population (i.e., Not A-M-C-C; N=291-33=258):

Among this group, $C_{avg}$ values are available in 224 patients.

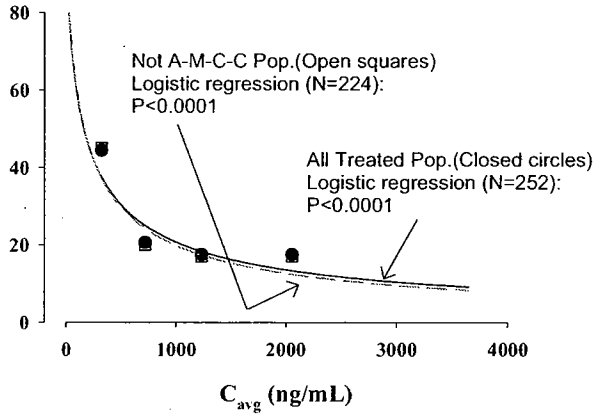
Clinical failure rate in 4 quartiles of $C_{avg}$ in A-M-C (N=28) vs. Not A-M-C-C (N=224)

| | Q1 (N=63) | Q2 (N=63) | Q3 (N=63) | Q4 (N=63) |
|---|---|---|---|---|
| A-M-C-C (N=28) | 50% (8/16) | 43% (3/7) | 33.3% (1/3) | 0% (0/2) |
| Not A-M-C-C (N=224) | 43% (20/47) | 18% (10/56) | 17% (10/60) | 18% (11/63) |
| Total (N=252) | 44.4% (28/63) | 20.6% (13/63) | 17.5% (11/63) | 17.5% (11/63) |

Clinical failure rate in Q1 vs. Q2-Q4 of $C_{avg}$ in A-M-C (N=45) vs. Not A-M-C (N=207)

| | Q1 (N=63) | Q2-Q4 (N=189) |
|---|---|---|
| A-M-C (N=28) | 50% (8/16) | 33% (4/12) |
| Not A-M-C (N=224) | 43% (20/47) | 18% (31/177) |
| Total (N=252) | 44.4% (28/63) | 19% (35/189) |

Logistic regression for Clinical Failure vs. $C_{avg}$ in this sub population



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/s/
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Kristen Miller
6/14/2006 12:43:39 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

# FACSIMILE TRANSMITTAL SHEET

**DATE:** June 5, 2006

| | |
|---|---|
| **To:** Todd Paporello, Pharm.D. | **From:** Kristen Miller, Pharm.D. |
| **Company:** Schering | Division of Special Pathogen and Transplant Products |
| **Fax Number:** 908-740-6500 | **Fax Number:** 301-796-9882 |
| **Phone Number**: 908-740-4252 | **Phone Number:** 301-796-0762 |

**Subject:** Comments and requests regarding NDAs 22-003 and 22-027

**Total no. of pages including cover:** 3

**Comments:** Concur:

| | |
|---|---|
| Maureen Tierney, M.D. | Medical Officer |
| Leonard Sacks, M.D. | Medical Team Leader |
| Karen Higgins, Sc.D. | Statistics Team Leader |
| Seong Jang, Ph.D. | Clinical Pharmacologist Reviewer |
| Philip Colangelo, PhD, PharmD | Clinical Pharmacologist Team Leader |

**Document to be mailed:** ☐ YES ☑ NO

Please refer to your new drug applications (NDAs) 22-003 and 22-027 for Noxafil® (posaconazole) Oral Suspension submitted on December 22, 2005. The Review Team has the following comments and requests:

We have more closely reviewed your submission that was discussed during the teleconference on Friday, May 26, 2006. Though the risk factors that you determined (GVHD, gender, and CMV status) do point to a group of posaconazole patients that have lower failure rate than similar fluconazole patients, they do not provide a reliable prediction for the occurrence of low posaconazole levels and, therefore, do not provide an adequate fluconazole group for comparison. In fact, the exposure-response (E-R) relationships are similar between the subgroup that you determined to be at high risk to the subgroup that excludes these patients, indicating that the E-R relationship was not confounded by these risk factors.

As we discussed in the meeting on Friday, May 26, there are other risk factors that may be considered when trying to more accurately model the development of low posaconazole levels (these are listed below); however, as we looked more closely at potential models, we were unable to come up with an adequate model and are concerned that you will also not be able to come up with one. Therefore, it is up to you whether or not to continue to model the baseline risk factors. Please be aware that absent convincing evidence that baseline risk factors alone can explain the low posaconazole levels, which could then be used to define an adequate fluconazole group for comparison, we continue to be concerned that the low posaconazole levels are causing, at least in part, the low success rates in these subjects. Please consider how this can be addressed in labeling.

*Risk factors include body irradiation (BODYIRRD), central venous catheter at baseline (CATHCDBS), risk with donor (DONORCD), GVHD grade 3/4 (GVHDBS), baseline aspergillus antigen (MAXASPAG), neutropenia at baseline (NEUTPTBS), oral swish for yeast (ORALYTBS), ECOG status at baseline (PRFRSTBS), race (RACE), and time from transplant to baseline (TRANDAY).*

Additionally, please do separate analyses of the following:

- levels versus diarrhea
- acute graft versus host disease (GVHD) Grades 3 and 4 separate from Grade 2.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-0762 if you have any questions.

Kristen Miller, Pharm.D.
Regulatory Health Project Manager

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Kristen Miller
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4 Page(s) Withheld

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

6 § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-_____*

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Antimicrobial Products**

## FACSIMILE TRANSMITTAL SHEET

**DATE:** May 23, 2006

| | |
|---|---|
| **To:** Todd Paporello, Pharm.D. | **From:** Kristen Miller, Pharm.D. |
| **Company:** Schering | Division of Special Pathogen and Transplant Products |
| **Fax Number:** 908-740-6500 | **Fax Number:** 301-796-9882 |
| **Phone Number**: 908-740-4252 | **Phone Number:** 301-796-0762 |

**Subject:** PK request regarding NDAs 22-003 and 22-027

**Total no. of pages including cover:**

**Comments:** Concur:

| | |
|---|---|
| Philip Colangelo, Pharm.D., Ph.D. | Clinical Pharmacology Team Leader |
| Seong Jang, Ph.D. | Clinical Pharmacology Reviewer |
| Leonard Sacks, M.D. | Clinical Team Leader |
| Maureen Tierney, M.D. | Medical Officer |
| Karen Higgins, Sc.D. | Statistics Team Leader |
| Jyoti Zalkikar, Ph.D. | Statistics Reviewer |

**Document to be mailed:** ☐ YES ☑ NO

Please refer to your new drug applications (NDAs) 22-003 and 22-027 for Noxafil® (posaconazole) Oral Suspension submitted on December 21, 2005. In the process of completing their review, our clinical pharmacologists, Dr. Jang and Dr. Colangelo have determined that there is a impressive difference in the clinical outcome and incidence of proven/probable IFI in the lowest quartile of patients (based on posaconazole levels) as opposed to the three higher quartiles of posaconazole patients or to the comparator in Study 98-316.

Dr. Jang composed the following questions along with the accompanying report. We are requesting the telecon scheduled for this Friday, May 26, 2006 in order to discuss this finding. We are hoping that you will be able to help us answer the questions below. Also attached are the datasets Dr. Jang used to examine this information.

1. Is the exposure-response relationship confounded by any other factors (for example food intake, disease severity, treatment period, baseline factors, etc.)?

2. Are there other outcome measures that show a similar pattern to that seen for Clinical Failure and Proven/Probable (PP) invasive fungal infections (IFIs) during the Primary Time Period?

3. Can you define four comparable comparator groups for the four posaconazole-exposure groups using baseline data including disease severity so that the efficacy of posaconazole of these groups can be considered relative to the control? This will help us determine if it is possibly the levels of posaconazole obtained in these groups or mainly the baseline variables that are causing the lower efficacy (i.e., higher incidence of clinical failure and P/P IFIs) compared with higher exposure group?

4. Is there any way to sort out the patients who will be exposed to low plasma levels of posaconazole? Is there any way to check to the baseline disease severity or the ability for food intake? Should plasma levels of posaconazole be measured during the first one or two weeks after the beginning of the treatment?

5. What can be done to the low exposure group of patients to improve efficacy?

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-0762 if you have any questions.

_____

Kristen Miller, Pharm.D.
Regulatory Health Project Manager

15 Page(s) Withheld

8 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-*_____

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Kristen Miller
5/23/2006 12:35:32 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

# FACSIMILE TRANSMITTAL SHEET

**DATE:** May 23, 2006

| | |
|---|---|
| **To:** Todd Paporello, Pharm.D. | **From:** Kristen Miller, Pharm.D. |
| **Company:** Schering | Division of Special Pathogen and Transplant Products |
| **Fax Number:** 908-740-6500 | **Fax Number:** 301-796-9882 |
| **Phone Number**: 908-740-4252 | **Phone Number:** 301-796-0762 |

**Subject:** Micro regarding annotated labeling (NDAs 22-003 and 22-027)

**Total no. of pages including cover:** 3

**Comments:** Concur:

Shukal Bala, Ph.D. — Microbiology Team Leader
Kalavati Suvarna, Ph.D. — Microbiology Reviewer

**Document to be mailed:** ☐ YES ☑ NO



Please refer to your new drug applications (NDAs) 22-003 and 22-027 for Noxafil ® (posaconazole) Oral Suspension submitted on December 22, 2005. Please also refer to your

May 8 and 16, 2006 submissions providing annotated labeling for the MICROBIOLOGY section. The Review Team has the following request:

> Your May 8 and 16, 2006 submissions provide annotated labeling for the MICROBIOLOGY/Mechanism of Action and Activity in vitro and in vivo subsections of the labeling. Please provide us with annotations to the actual study reports or publications for the remaining subsections (Drug Resistance and Antifungal Drug Combinations).

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-0762 if you have any questions.

_____

Kristen Miller, Pharm.D.
Regulatory Health Project Manager

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Kristen Miller
5/23/2006 12:03:16 PM
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Center for Drug Evaluation and Research
Office of Antimicrobial Products

# FACSIMILE TRANSMITTAL SHEET

**DATE:** May 15, 2006

| | |
|---|---|
| **To:** Todd Paporello, Pharm.D. | **From:** Kristen Miller, Pharm.D. |
| **Company:** Schering | Division of Special Pathogen and Transplant Products |
| **Fax Number:** 908-740-6500 | **Fax Number:** 301-796-9882 |
| **Phone Number**: 908-740-4252 | **Phone Number:** 301-796-0762 |

**Subject:** Request regarding NDAs 22-003 and 22-027

**Total no. of pages including cover:** 3

**Comments:** Concur:

| | |
|---|---|
| Maureen Tierney, M.D. | Medical Officer |
| Karen Higgins, Sc.D. | Statistics Team Leader |

**Document to be mailed:** ☐ YES ☑ NO

Please refer to your new drug applications (NDAs) 22-003 and 22-027 for Noxafil ® (posaconazole) Oral Suspension submitted on December 22, 2005. The Review Team has the following requests and questions:

1. The clinical outcome tables G.3, G.3.1a, and I.3.1aa have different clinical outcomes than in the study report. Please explain the difference and list the categories of which patients are now considered failures.

2. In every table separating out the POS/ITRA results, the results comparing POS to FLU should only compare POS at the FLU sites to FLU. We can figure those results appropriately for the tables but please provide ASAP the Time to IFI and Time to Death for the POS/FLU at the FLU sites only.

3. Is the Clinical Outcome for the Oral treatment Phase or the for the Day 100 phase? Could you please provide the Clinical Outcome for both?

4. For Study C98-316, please provide the same analysis with the same definition of clinical failure used for tables G.3, etc. for Study PO1899. For Study PO1899, please provide a similar background for these outcomes as requested in Question 1 above.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-0762 if you have any questions.

_____

Kristen Miller, Pharm.D.
Regulatory Health Project Manager

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Kristen Miller
5/15/2006 01:09:16 PM
CSO

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Antimicrobial Products**

## FACSIMILE TRANSMITTAL SHEET

**DATE:** April 28, 2006

| | |
|---|---|
| **To:** Todd Paporello, Pharm.D. | **From:** Kristen Miller, Pharm.D. |
| **Company:** Schering Corporation | Division of Special Pathogen and Transplant Products |
| **Fax Number:** 908-740-6500 | **Fax Number:** 301-796-9882 |
| **Phone Number**: 908-740-4252 | **Phone Number:** 301-796-0762 |

**Subject:** Request regarding NDAs 22-003 and 22-027

**Total no. of pages including cover:** 4

**Concurrence:**

| | |
|---|---|
| Maureen Tierney, M.D. | Medical Officer |
| Kalavati Suvarna, Ph.D. | Microbiology Reviewer |

**Document to be mailed:** ☐ YES ☑ NO

Please refer to your new drug applications (NDAs) 22-003 and 22-027 for Noxafil ® (posaconazole) Oral Suspension submitted on December 22, 2005. The Review Team requests that you provide responses for the information requests (listed below) by Monday, May 8, 2006.

Clinical

1. As was requested for study C/I98-316, we request an analysis of clinical failure as a composite end-point of proven/probable IFIs and for empiric use of antifungal agents, deaths, and early discontinuations (including AEs) for all treated subjects during the primary time period.
   In addition, we request a similar failure/success analysis while on treatment for POSACONAZOLE VS FLUCONAZOLE VS ITRACONAZOLE for study P01899 during the primary time period.

2. In the aforementioned analyses provided for C/I98-316, the following table was provided as an adjunct to Table G.3.3

   Table G.3.3.1.Treatment Failure During Primary Time Period by Criteria Met and by Treatment Group

| | IFI | Empiric use of AF | Discontinued Treatment |
|---|---|---|---|
| Posaconazole | 15 | 25 | 89 |
| Fluconazole | 27 | 29 | 97 |

   Does the "Discontinued Treatment" column include death? Did the clinical failure for tables G.3.3 and G.3.4. include death?

3. In study P01899, almost of all the analyses are presented as POSACONAZOLE VS FLU/ITRA. We request that you provide the major analyses listed below for POSACONAZOLE VS FLUCONAZOLE VS ITRACONAZOLE.

   - Incidence of IFI in the Oral Treatment Phase and at 100 days, both total and broken down by organism
   - IFI broken down by Proven/Probable, total and by organism
   - Deaths (All Cause especially)
   - Time to Death
   - Time to IFI

4. For the Centers where itraconazole was the standard azole, we request the above analyses for Posaconazole versus Itraconazole at those sites, individually and pooled.

Microbiology

1. In studies C/I98-316 and P01899, the presence of Aspergillus antigen in serum and BAL samples was tested using the [redacted] Aspergillus EIA test manufactured by [redacted] laboratory. The test kit manufactured by [redacted] is not approved in the US. Please provide the following information for our review:

   (a) the performance characteristics of the test, and
   (b) the basis for an optical density index of $\geq 0.5$ as the threshold for categorizing the test as positive

2. Please provide details of the microbiological criteria used to determine probable infections in the patients listed below:

| **Study C/I98-316** |
|---|
| C012000014 |
| C025000034 |
| I 028000785 |
| C009000341 |
| I004000048 |
| **Study P01899** |
| 0125001109 |

3. The microbiology section of the draft product labeling (PI) includes annotations to summary sections in module 2 of the submission. Please provide the microbiology section of the draft PI with annotations to the actual study reports or publications.

Please feel free to contact me at 301-796-0762 if you have any questions.

Kristen Miller, Pharm.D.
Regulatory Health Project Manager

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/s/
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Brenda Marques
4/28/2006 03:04:19 PM
On behalf of Kristen Miller

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

# FACSIMILE TRANSMITTAL SHEET

**DATE:** April 24, 2006

| | |
|---|---|
| **To:** Todd Paporello, Pharm.D. | **From:** Kristen Miller, Pharm.D. |
| **Company:** Schering | Division of Special Pathogen and Transplant Products |
| **Fax Number:** 908-740-6500 | **Fax Number:** 301-796-9882 |
| **Phone Number**: 908-740-4252 | **Phone Number:** 301-796-0762 |

**Subject:** Request regarding Non-inferiority Margins

**Total no. of pages including cover:** 3

**Comments:** Concur:
Karen Higgins Sc.D. Statistics Team Leader

**Document to be mailed:** ☐ YES ☑ NO

Please refer to your new drug applications (NDAs) 22-003 and 22-027 for Noxafil ® (posaconazole) Oral Suspension submitted on December 22, 2005. The Review Team has the following request:

We have been unable to find any discussion as to the appropriateness of the pre-specified non-inferiority margins used in your phase 3 studies. Please provide a discussion of why posaconazole should be considered effective from the results of these studies including a justification for your choice of non-inferiority margins for each study or direct us to its location in the submission.

As discussed in the ICH guidance documents "E9 Statistical Principles for Clinical Trials" and "E10 Choice of Control Group and Related Issues in Clinical Trials" (located at www.fda.gov/cder/guidance/index.htm) a non-inferiority margin should be defined as "the largest difference that can be judged as being clinically acceptable and should be smaller than differences observed in superiority trials of the active comparator." It "cannot be greater than the *smallest effect size that the active drug would be reliably expected to have* compared with placebo in the setting of the planned trial." Furthermore, 21CFR314.126(b)(2)(iv) states the following:

> If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-0762 if you have any questions.

_____

Kristen Miller, Pharm.D.
Regulatory Health Project Manager

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/s/

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Kristen Miller
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CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-003
NDA 22-027

Schering Corporation
Attention: Todd Paporello, Pharm.D.
Regulatory Affairs Manager, Global Regulatory Affairs
2000 Galloping Hill Roads
Kenilworth, NJ 07033

Dear Dr. Paporello:

Please refer to your February 23, 2006 correspondence requesting a meeting to discuss the status of the ongoing NDA reviews for Noxafil ® (posaconazole) Oral Suspension (NDAs 22-003 and 22-027), in accordance with 21 CFR 314.102(c).

The following are the Division's responses to the questions submitted for the proposed meeting. If our responses are clear to you and you determine that further discussion is not required, you have the option of canceling the teleconference scheduled for March 27, 2006. Please note that if there are any major changes to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.

1. Is the Division on target for a June 22, 2006 Action Date for NDA 22-003 (prophylaxis) and an October 20, 2006 Action Date for NDA 22-027 (OPC)? Has the Division identified any barriers to achieving this target? If so, please elaborate.

   *The Division is currently on target for a June 22, 2006 action date for NDA 22-003 (for prophylaxis) and an October 20, 2006 action date for NDA 22-027 (OPC). No barriers to achieving these targets have been identified to date. The reviews, however, have not been finalized and unforeseen issues may arise that require further discussion or data as the review progresses.*

2. Does the Division continue to believe that an Advisory Committee Meeting will not be necessary in order to approve posaconazole for the prophylaxis and OPC indications?

   *Currently, no issues have arisen that would lead the Division to believe that an Advisory Committee Meeting is necessary to discuss the data submitted for either application. However, full review of the applications is needed to definitively state that an Advisory Committee Meeting will not be necessary in order to approve posaconazole for the prophylaxis and OPC indications.*

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/s/

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Kristen Miller
3/20/2006 05:45:26 PM
CSO

Renata Albrecht
3/21/2006 08:25:17 AM
MEDICAL OFFICER

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

**Date:** March 9, 2006
**To:** NDAs 22-003 and 22-027/ Schering-Plough
**From:** Kristen Miller, Pharm.D.
**Subject:** Administrative split of NDA 22-003

On December 21, 2005, Schering submitted a new drug application (NDA) for Noxafil® (posaconazole) Oral Suspension, 200mg/5mL. This application contained two indications: prophylaxis of invasive fungal infections and treatment of oropharyngeal candidiasis. NDA 22-003 was split for our administrative purposes and a second NDA number, 22-027 was assigned. NDA 22-003 was granted a priority review for the indication of prophylaxis of invasive fungal infections, and NDA 22-027 was granted a standard review for the indication of treatment of oropharyngeal candidiasis. Schering was notified of this split in the February 8, 2006, acknowledgement letter.

**MEMORANDUM**

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/s/
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Kristen Miller
3/9/2006 03:27:37 PM
CSO

# NDA REGULATORY FILING REVIEW
**(Including Memo of Filing Meeting)**

NDA # 22-003 & 22-027 Supplement # N/A Efficacy Supplement Type SE- N/A

Trade Name: Noxafil
Established Name: posaconazole
Strengths: 200mg/ 5mL Oral Suspension

Applicant: Schering Corporation
Agent for Applicant:

Date of Application: December 21, 2005
Date of Receipt: December 22, 2005
Date clock started after UN: N/A
Date of Filing Meeting: February 6, 2006
Filing Date: February 20, 2006
Action Goal Date (optional):

User Fee Goal Date: 22-003: June 22, 2006
22-027: October 22, 2006

Indication(s) requested: 22-003: Prophylaxis of invasive fungal infections
22-027: Treatment of oropharyngeal candidiasis

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

***NOTE:***

*(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*

*(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

☐ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ 22-027 P ☒ 22-003
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

***NOTE:*** *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication*

*for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  **If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  **If an electronic NDA, all forms and certifications must be in paper and require a signature.**
  Which parts of the application were submitted in electronic format? All forms and certifications.

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☒
  **If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.**

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  ***NOTE:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐

**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

***NOTE:*** *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☐
  Requested: 3/6/06 ☒ NO

  **(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)**
  **NOTE:** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 51,662

- End-of-Phase 2 Meeting(s)? Date(s) December 13, 2000 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) October 25, 2005 NO ☐
  If yes, distribute minutes before filing meeting.

## Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

## If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

## Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

## Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

Shukal Bala, Ph.D.
Kalavati Suvarna, Ph.D.
Diana Willard
Kristen Miller, Pharm.D.

ASSIGNED REVIEWERS (including those not present at filing meeting):

| **Discipline** | **Reviewer** |
|---|---|
| Medical: | Maureen Tierney, M.D.<br>Regina Alivisatos, M.D. |
| Statistical: | Jyoti Zalkikar, Ph.D.<br>Cheryl Dixon, Ph.D |
| Pharmacology: | Owen McMaster, Ph.D. |
| Chemistry: | Mark Seggel, Ph.D. |
| Biopharmaceutical: | Seong Jang, Ph.D.<br>Dakshina Chilukuri, Ph.D. |
| Microbiology, clinical: | Kalavati Suvarna, Ph.D.<br>Lynn Steele-Moore |
| DSI: | Karen Storms |
| Regulatory Project Management: | Kristen Miller, Pharm.D. |
| Other Consults: | DMETS, DDMAC |

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO ☒
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Microbiology YES ☐ NO ☐

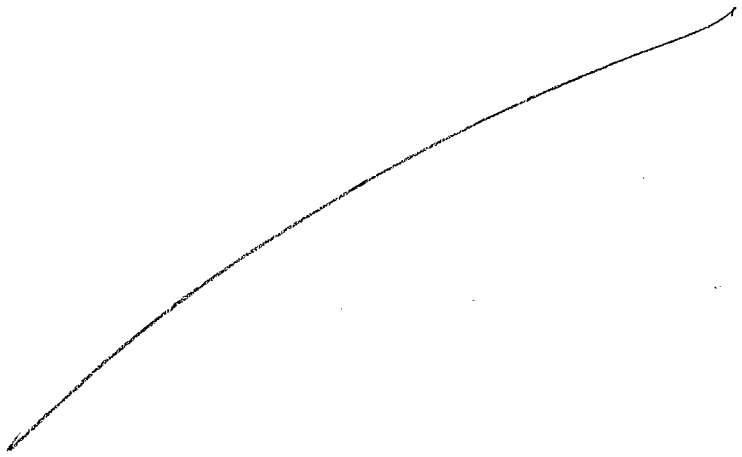
ELECTRONIC SUBMISSION:
Any comments:

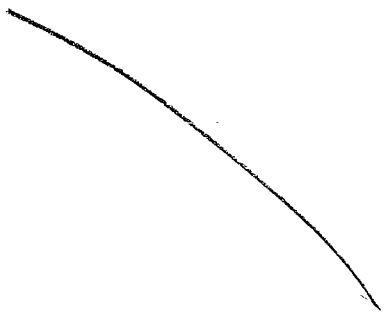
REGULATORY CONCLUSIONS/DEFICIENCIES:
**(Refer to 21 CFR 314.101(d) for filing requirements.)**

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List:





We also request that you submit the following datasets to support the population PK analysis in Study P01899:

- All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line.

**ACTION ITEMS:**

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3.☒ Convey document filing issues/no filing issues to applicant by Day 74.

Sent to Schering on March 2, 2006.

Kristen Miller, Pharm.D.
Regulatory Project Manager, HFD-590

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/s/
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Kristen Miller
3/6/2006 03:38:04 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-003
NDA 22-027

Schering Corporation
Attention: Todd Paporello, Pharm.D.
Regulatory Affairs Manager, Global Regulatory Affairs
2000 Galloping Hill Roads
Kenilworth, NJ 07033

Dear Dr. Paporello:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Noxafil ® (posaconazole) Oral Suspension.

We also refer to your February 23, 2006 correspondence, received February 24, 2006 requesting a meeting to provide a brief report on the status of the ongoing NDA reviews for posaconazole, in accordance with 21 CFR 314.102(c).

Based on the statement of purpose we consider the meeting a type B meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

| | |
|---|---|
| Date: | March 27, 2006 |
| Time: | 11:30 AM – 12:30 PM |
| Location: | Teleconference |
| Number: | 866-755-7891 |
| Pass code: | [redacted] |

Proposed CDER participants:

| | |
|---|---|
| Edward Cox, M.D. M.P.H. | Deputy Director- Office of Antimicrobial Products |
| Renata Albrecht, M.D. | Director - Division of Special Pathogen and Transplant Products (DSPTP) |
| Steven Gitterman, M.D. | Deputy Director- DSPTP |
| Leonard Sacks, M.D. | Clinical Team Leader |
| Regina Alivisatos, M.D. | Clinical Reviewer |
| Maureen Tierney, M.D. | Clinical Reviewer |
| Elizabeth O'Shaughnessy, M.D. | Clinical Reviewer |
| Philip Colangelo Ph.D | Clinical Pharmacology Team Leader |
| Seong Jang, Ph.D. | Clinical Pharmacology Reviewer |
| Dakshina Chilukuri, Ph.D. | Clinical Pharmacology Reviewer |

| | |
|---|---|
| Karen Higgins, Sc.D. | Statistics Team Leader |
| Jyoti Zalkikar, Ph.D. | Statistics Reviewer |
| Cheryl Dixon, Ph.D. | Statistics Reviewer |
| William Taylor, Ph.D. | Pharmacology Toxicology Team Leader |
| Owen McMaster, Ph.D. | Pharmacology Toxicology Reviewer |
| Shukal Bala, Ph.D. | Microbiology Team Leader |
| Kalavati Suvarna, Ph.D. | Microbiology Reviewer |
| Lynn Steele-Moore | Microbiology Reviewer |
| Mark Seggel, Ph.D. | Chemistry Reviewer |
| Kristen Miller, Pharm.D | Regulatory Project Manager |

Provide the background information for this meeting at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, we may cancel or reschedule the meeting.

If you have any questions, please call me at (301) 796-0762.

Sincerely,

*{See appended electronic signature page}*

Kristen Miller, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

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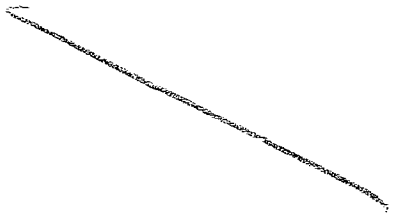
Kristen Miller
3/2/2006 02:49:50 PM



b. Please address the reason(s) for the increase in posaconazole oral clearance, reduction of half-life, and decrease in plasma exposure to posaconazole following co-administration of rifabutin (Study I96207) and phenytoin (Study C96201). The mechanism for the decrease in posaconazole exposure by rifabutin and phenytoin appears important to address and important to determine if further drug-drug interaction studies between other CYP3A4 enzyme inducers and posaconazole may be needed.

c. Please compare the CYP3A inhibition potency of posaconazole relative to other triazole antifungal agents such as ketoconazole, itraconazole, and voriconazole. The magnitude of CYP3A inhibition of posaconazole relative to other triazole antifungal agents can be used to address interactions between posaconazole and other drugs which are metabolized by CYP3A using the known interactions between other triazole antifungal agents and CYP3A substrates. One of the recommended ways to compare the relative magnitude of CYP3A enzyme inhibition by posaconazole is to evaluate the effect of posaconazole on the PK of oral midazolam, which is a sensitive probe of hepatic and intestinal CYP3A enzyme activity, in a healthy volunteer study.

2. We also request that you submit the following datasets to support the population PK analysis in Study P01899:

a. All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

b. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of these applications and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the applications.

If you have any questions, please call Kristen Miller, Pharm.D., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

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Renata Albrecht
3/2/2006 08:50:43 AM

Please cite the NDA numbers listed above at the top of the first page of all submissions to these applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Division of Special Pathogen and Transplant Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call me, at (301) 796-0762.

Sincerely,

*{See appended electronic signature page}*

Kristen Miller, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

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Kristen Miller
2/8/2006 01:50:17 PM

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

| Application Information | | | |
|---|---|---|---|
| NDA 22-003 | Efficacy Supplement Type SE- N/A | Supplement Number- N/A | |
| Drug: Noxafil (posaconazole) Oral Suspension | | Applicant: Schering | |
| RPM: Kristen Miller | | HFD- 590 | Phone # 301-796-0762 |

| | |
|---|---|
| Application Type: ( X ) 505(b)(1) ( ) 505(b)(2)<br>(This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)<br><br>**If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.**<br><br>( ) Confirmed and/or corrected | Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s): N/A |

| | |
|---|---|
| ❖ Application Classifications: | |
| • Review priority | ( ) Standard ( X ) Priority |
| • Chem class (NDAs only) | Class 1 (NME) |
| • Other (e.g., orphan, OTC) | N/A |
| ❖ User Fee Goal Dates | June 22, 2006 |
| ❖ Special programs (indicate all that apply) | ( X ) None<br>Subpart H<br>( ) 21 CFR 314.510 (accelerated approval)<br>( ) 21 CFR 314.520 (restricted distribution)<br>( ) Fast Track<br>( ) Rolling Review<br>( ) CMA Pilot 1<br>( ) CMA Pilot 2 |
| ❖ User Fee Information | |
| • User Fee | ( X ) Paid UF ID number 3006318 |
| • User Fee waiver | ( ) Small business<br>( ) Public health<br>( ) Barrier-to-Innovation<br>( ) Other (specify) |
| • User Fee exception | ( ) Orphan designation<br>( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions)<br>( ) Other (specify) |
| ❖ Application Integrity Policy (AIP) | |
| • Applicant is on the AIP | ( ) Yes ( X ) No |

| | |
|---|---|
| • This application is on the AIP | ( ) Yes ( **X** ) No |
| • Exception for review (Center Director's memo) | N/A |
| • OC clearance for approval | N/A |
| ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent. | ( **X** ) Verified |
| ❖ Patent | |
| • Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. | ( **X** ) Verified |
| • Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | 21 CFR 314.50(i)(1)(*i*)(A)<br>( ) Verified<br><br>21 CFR 314.50(i)(1)<br>( ) (ii) ( ) (iii) |
| • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | |
| • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).* | ( ) N/A (no paragraph IV certification)<br>( ) Verified |
| • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.<br><br>Answer the following questions for each paragraph IV certification:<br><br>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?<br><br>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).<br><br>*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*<br><br>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?<br><br>*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*<br><br>*If "**No**," continue with question (3).*<br><br>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? | ( ) Yes ( ) No<br><br>( ) Yes ( ) No<br><br>( ) Yes ( ) No |

| | |
|---|---|
| (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).<br><br>*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* | |
| (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?<br><br>*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*<br><br>*If "**No**," continue with question (5).* | ( ) Yes ( ) No |
| (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?<br><br>(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).<br><br>*If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*<br><br>*If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.* | ( ) Yes ( ) No |

| | |
|---|---|
| ❖ Exclusivity (approvals only) | |
| • Exclusivity summary<br>• Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) | X- 5/31/06<br><br>N/A |
| • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.* | ( ) Yes, Application #_____<br>( **X** ) No |
| ❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)* | X- Filing Review: 3/6/06 |

| General Information | |
|---|---|
| ❖ Actions | |
| • Proposed action | ( **X** ) AP ( ) TA ( ) AE ( ) NA |
| • Previous actions (specify type and date for each action taken) | ~~(posaconazole)~~ received an AE on 6/10/04 |
| • Status of advertising (approvals only) | **(X)**Materials requested in AP letter<br>( ) Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) | ( **X** ) Yes ( ) Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated | ( ) None<br>( **X** ) Press Release<br>( ) Talk Paper<br>( ) Dear Health Care Professional Letter |
| ❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)) | |
| • Most recent applicant-proposed labeling | X- final (9/15/06) |
| • Original applicant-proposed labeling | X |
| • Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)* | X- Consults<br>DDMAC Review: 6/20/06<br>DMETS Review: 5/23/06<br>DMETS name consult- 8/25/06<br>DMETS name review- 8/30/06 |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | X- Voriconazole (5/19/06), Fluconazole (10/7/04), Itraconazole (9/24/03) |
| ❖ Labels (immediate container & carton labels) | |
| Applicant proposed | X- 12/21/06 and 6/16/06 |
| • Reviews | See DMETS reviews under labeling |
| ❖ Post-marketing commitments | |
| • Agency request for post-marketing commitments | X- 6/20/06, 8/23/06 |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | X – 6/21/06 |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) | 2/8/06 (Acknowledge letter)<br>3/2/06 (Filing letter- issues noted)<br>3/21/06 (Review update letter)<br>4/24/06 (statistical request fax)<br>4/28/06, 5/15/06, 5/17/06, 5/23/06 (clinical info request faxes)<br>5/23/06, 6/5/06, 6/14/06 (PK request fax)<br>5/30/06 (Label comments) |
| ❖ Memoranda and Telecons | X- 3/9/06 (Admin split MEMO)<br>6/22/06 (missing action date t-con) |
| ❖ Minutes of Meetings | |
| • EOP2 meeting (indicate date) | X- 12/13/00 (Schering's minutes) |
| • Pre-NDA meeting (indicate date) | X- 10/25/05 |
| • Pre-Approval Safety Conference (indicate date; approvals only) | X- 6/9/06 |

| | |
|---|---|
| • Other | N/A |
| ❖ Advisory Committee Meeting | |
| • Date of Meeting | N/A |
| • 48-hour alert | N/A |
| ❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable) | N/A |
| **Summary Application Review** | |
| ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)* | X- 9/15/06 |
| **Clinical Information** | |
| ❖ Clinical review(s) *(indicate date for each review)* | X- 9/15/06 |
| ❖ Microbiology (efficacy) review(s) *(indicate date for each review)* | X- 6/20/06<br>X- 6/21/06 (Team Leader Review) |
| ❖ Safety Update review(s) *(indicate date or location if incorporated in another review)* | See Clinical Review |
| ❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)* | N/A |
| ❖ Pediatric Page(separate page for each indication addressing status of all age groups) | X – 5/30/06 |
| ❖ Statistical review(s) *(indicate date for each review)* | X- 6/22/06, 9/1/06 (addendum) |
| ❖ Biopharmaceutical review(s) *(indicate date for each review)* | X- 6/20/06 |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling | N/A |
| ❖ Clinical Inspection Review Summary (DSI) | |
| • Clinical studies | Information request- 6/26/06<br>Info request addendum- 6/26/06<br>Consult request – 6/30/06<br>Consult request- 7/13/06<br>Review, inspections – 9/7/06<br>Memo- exclude site- 9/7/06<br>Review including site- 9/7/07 |
| • Bioequivalence studies | N/A |
| **CMC Information** | |
| ❖ CMC review(s) *(indicate date for each review)* | X- 6/21/06 |
| ❖ Environmental Assessment | |
| • Categorical Exclusion *(indicate review date)* | X – 12/20/05 |
| • Review & FONSI *(indicate date of review)* | N/A |
| • Review & Environmental Impact Statement *(indicate date of each review)* | N/A |
| ❖ Microbiology (validation of sterilization & product sterility) review(s) | N/A |
| ❖ Facilities inspection (provide EER report) | Date completed: 5/31/06<br>**( X )** Acceptable<br>**( )** Withhold recommendation |
| ❖ Methods validation | **( )** Completed<br>**( )** Requested<br>**( X )** Not yet requested |
| **Nonclinical Pharm/Tox Information** | |
| ❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | X- 6/20/06 |
| ❖ Nonclinical inspection review summary | N/A |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | N/A |
| ❖ CAC/ECAC report | |

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/s/
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Kristen Miller
9/15/2006 03:24:44 PM

**Table 23: Distribution of Clinical Failure as defined by the FDA Review Team (All Randomized Patients)**

| | Number (%)of subjects | | | | |
|---|---|---|---|---|---|
| Clinical Outcome of oral phase plus 7 days | POS (N =304) n (%) | FLU/ITZ (N=298) n (%) | Difference (POS-FLU/ITZ)** | 95.13% confidence interval** | P-value** |
| Clinical Success | 166 (55%) | 126 (42%) | 12.2% | (4.3, 20.1) | 0.002 |
| Clinical Failure | 138 (45%) | 172 (58%) | | | |
| Due to | | | | | |
| IFI | 7 | 25 | | | |
| Death* | 18 | 26 | | | |
| Use of Systemic Therapy | 63 | 88 | | | |
| Not followed/discontinued | 51 | 35 | | | |

*: For study P01899, 1 posaconazole patient and 2 control patients were counted as both IFI and death. All other outcomes are ranked by order in the table.

**: Difference, p-value and 95.13% confidence interval of the difference (POS – FLU/ITZ) using a normal approximation adjusted by the control-site and baseline stratification factor as described by Fleiss[6].

The reviewers conducted additional sensitivity analyses of clinical outcome defining all treatment discontinuations as failures and defining no treatment discontinuations as failures and similar results were obtained.

Given that this study used two different controls, based on site, it is of importance to check the consistency of results by control used in order to assess if pooling the information is valid. The following table reports the reviewers' analysis of clinical failure by each type of comparator used. Though the sites that used itraconazole had lower success rates, the treatment effect (difference between posaconazole and control) is similar. Test for homogeneity of odds ratio did not reject the null hypothesis of homogeneity.

**Table 24: Clinical failure by comparator used**

| **Clinical Outcome** | **Fluconazole Sites** | | **Itraconazole sites** | |
|---|---|---|---|---|
| | **POS** N=239 | **FLU** N=240 | **POS** N=65 | **ITZ** N=58 |
| Failure | 99 (41) | 132 (55) | 39 (60) | 40 (69) |
| Success | 140 (59) | 108 (45) | 26 (40) | 18 (31) |
| Difference in success rates, CI[#] and p-value | **13.6** (4.7 22.4) | 0.003 | **9.0** (-7.9, 25.8) | 0.3004 |

#95% confidence intervals (POS – Control) and p-value based on a normal approximation adjusted by the baseline stratification factor as described by Fleiss[6].

## 3.2 Evaluation of Safety

The reader is referred to safety review by the medical officer Dr. Maureen Tierney. The following is a brief summary of that review.

Posaconazole is a relatively well tolerated azole with some of the same safety concerns as other members of the azole class and some possibly unique safety issues.

- Increase in hepatic adverse events including elevation in liver function tests and rare cases of severe liver injury in patients with severe underlying comorbidity.

- Drug interaction with cyclosporine (and tacrolimus) which can lead to severe, even fatal, cyclosporine toxicity.

- Inhibitor of CYP3A4

- Similar rates of increase of >60msec of QTc from baseline and QTC over 500 msec in POS prophylaxis patients as those who received fluconazole. No similar events recorded in healthy subjects. One case of torsades de Pointes in posaconazole prophylaxis pool of patients with severe electrolyte abnormalities.

- Mild increase in incidence of significant hypokalemia (13%) in comparison to fluconazole (10%.)

- Increase in number of patients with pulmonary embolus in the post stem cell transplant patients with GVHD who received posaconazole in comparison to fluconazole (6 versus 0).

- Mild increase in TTP ( and overall thrombocytopenia) and HUS in the post stem cell transplant patients with GVHD who received posaconazole in comparison to fluconazole.

# 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

## 4.1 Gender, Race and Age

### 4.1.1 Study C/I98-316

The following table contains the results of the sponsor's clinical success endpoint and the sponsor's primary endpoint, proven or probable IFI breakthrough infections, for the subgroups of gender, race and age. For male subjects there appears to be little difference between the two treatments in either analysis. All the difference seen between the arms are with female subjects. A logistic model was run with gender and treatment and the interaction was not found to be significant. There was no strong trend seen in the breakdown by race, given that races other than Caucasian had fairly small sample sizes. There was also no strong trend with age when broken down by < 18, 18 – 65, and >= 65. Age or an interaction of treatment and age were also not significant when age was treated as a continuous variable in a logistic model.

**Table 25: Gender, Race and Age based subgroup analysis for Study C/I98-316 (All randomized Patients)**

| | Sponsor's Endpoint of Clinical Success* | | Sponsor's Primary Endpoint Proven or probable IFI** | |
|---|---|---|---|---|
| | Posaconazole | Fluconazole | Posaconazole | Fluconazole |
| Gender | | | | |
| Males | 133/203 (66) | 124/187 (66) | 11/203 (5) | 11/187 (6) |
| Females | 69/98 (70) | 65/112 (58) | 5/98 (5) | 16/112 (14) |
| | | | | |
| Race | | | | |
| Caucasian | 172/259 (66) | 154/246 (63) | 15/259 (6) | 21/246 (9) |
| Hispanic | 13/19 (68) | 15/24 (63) | 0/19 (0) | 3/24 (13) |
| Black | 10/12 (83) | 11/18 (61) | 0/12 (0) | 2/18 (11) |
| Asian | 5/9 (56) | 8/10 (80) | 1/9 (11) | 1/10 (10) |
| American Indian | 2/2 (100) | 1/1 (100) | 0/2 (0) | 0/1 (0) |
| | | | | |
| Age | | | | |
| < 18 | 2/4 (50) | 7/8 (88) | 1/4 (25) | 0/8 (0) |
| 18 to < 65 | 198/292 (68) | 180/286 (63) | 14/292 (5) | 25/286 (9) |
| >= 65 | 2/5 (40) | 2/5 (40) | 1/5 (20) | 2/5 (40) |

* Sponsor's defined clinical success. Subject is considered a failure if a proven or probable IFI is present, received more than 5 days of empiric treatment with another antifungal during the primary time period, not followed for the entire 16 weeks of scheduled follow-up, or died.

** Subject is considered a failure if proven or probable IFI is present. Results taken from table 17 in section 2.7.3 of sponsor's report.

### 4.1.2 Study P01899

The following table contains the results of the reviewers' primary endpoint, clinical success, and the sponsor's primary endpoint, proven or probable IFI breakthrough infections, for the subgroups of gender, race and age. There was no strong trend seen in the breakdown by gender or age. All the difference seen between arms for the reviewer's clinical success is coming from Caucasians. However, note that all other races had fairly small sample sizes.

**Table 26: Gender, Race and Age based subgroup analysis for Study P01899 (All randomized patients)**

| | Reviewer's Clinical Success* | | Sponsor's Primary Endpoint Proven or probable IFI** | |
|---|---|---|---|---|
| | POS | FLU/ITZ | POS | FLU/ITZ |
| Gender | | | | |
| Males | 91/158 (58) | 66/160 (41) | 3/158 (2) | 12/160 (8) |
| Females | 75/146 (51) | 60/138 (43) | 4/146 (3) | 13/138 (9) |
| | | | | |
| Race | | | | |
| Caucasian | 120/220 (55) | 89/231 (39) | 5/220 (2) | 20/231 (9) |
| Hispanic | 30/51 (59) | 28/47 (60) | 1/51 (2) | 2/47 (4) |
| Black | 9/16 (56) | 5/9 (56) | 0/16 (0) | 1/9 (11) |
| Asian | 2/13 (15) | 2/9 (22) | 1/13 (8) | 2/9 (22) |
| Other *** | 3/4 (75) | 2/2 (100) | 0/4 (0) | 0/2 (0) |
| | | | | |
| Age | | | | |
| < 18 | 5/8 (63) | 3/8 (38) | 1/8 (13) | 0/8 (0) |
| 18 to < 65 | 132/238 (55) | 95/223 (43) | 4/238 (2) | 18/223 (8) |
| >= 65 | 29/58 (50) | 28/67 (42) | 2/58 (3) | 7/67 (10) |

* Reviewer's defined clinical success where patients is a failure if a proven or probable IFI is present, received 4 or more days of empiric treatment with another antifungal for suspected IFI, use of IV alternative antifungal medication for >3 consecutive days or >= 10 cumulative days, discontinuation due to an AE regardless of determination of causality, discontinuation due to treatment failure, withdrawn from the study for any reason, lost to follow-up during the treatment phase (treatment plus 7 days) or death during the treatment phase.
** Subject is considered a failure if proven or probable IFI is present. Results taken from table 17 in section 2.7.3
*** Includes Native American, Indian and mixed race.

### 4.2 Other Special/Subgroup Populations

The sponsor felt that it was important for the studies to be balanced across treatment by Acute or Chronic GVHD for study C/I98-316 and by Acute Leukemia (new or primary relapse) or Myelodysplastic syndrome for study P01899 and therefore, conducted their randomization stratified by these factors. The following table, Table 27, reports the clinical success by these stratification factors used at randomization. Though the clinical success rate does vary slightly across strata, the treatment effect (difference between posaconazole and control) remains fairly constant.

**Table 27: Clinical success by stratification factors for Studies C/I98-316 and P01899 (All randomized patients)**

| | Clinical Success* | |
|---|---|---|
| | Posaconazole | Control |
| Study C/I98-316** | | |
| Acute GVHD | 123/202 (60.9) | 117/197 (59.3) |
| Chronic GVHD | 78/98 (79.6) | 72/100 (72.0) |
| Study P01899 | | |
| Acute Leukemia (new) | 116/213 (55.5) | 94/222 (42.3) |
| Acute Leukemia (primary relapse) | 22/42 (52.3) | 14/38 (36.8) |
| Myelodysplastic syndrome | 28/49 (57.1) | 18/38 (47.3) |

* Sponsor's defined clinical success for study C/I98-316. Reviewer's defined clinical success for study P01899 where patients is a failure if a proven or probable IFI is present, received 4 or more days of empiric treatment with another antifungal for suspected IFI, use of IV alternative antifungal medication for >3 consecutive days or >= 10 cumulative days, discontinuation due to an AE regardless of determination of causality, discontinuation due to treatment failure, withdrawn from the study for any reason, lost to follow-up during the treatment phase (treatment plus 7 days) or death during the treatment phase.

** 3 subjects did not have GVHD status reported.

# 5. SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues and Collective Evidence

### 5.1.1 Statistical Issues

There were a number of statistical issues discovered in the review of the two prophylaxis studies (C/I98-316 and P01899). They include

1> Definition of the primary analysis

2> Analysis of prophylaxis for aspergillosis alone

3> Non-inferiority design with comparators not approved for the indication sought by the applicant (namely, all invasive fungal infections)

4> Justification for the non-inferiority margin

5> Limitations of statistical methods to resolve issues of concentration-response relationship found by the clinical pharmacology reviewer

These issues as well as a labeling comment will be discussed here.

1. Definition of the primary analysis:

As mentioned in section 3.1, the review team had major concerns regarding the sponsor's primary efficacy endpoint. The applicant defined the primary efficacy endpoint as occurrence of IFI in all randomized patients during the pre-specified

(primary) time period. Though this endpoint is considered clinically meaningful, the concern arises regarding the details of the analysis and how subjects with essentially missing data are handled. For instance, subjects who die during the primary time period can no longer have a breakthrough IFI infection and this constitutes informative censoring. Considering these patients as "successes" may lead to biased estimates of the treatment effect. Therefore the review team decided it was more appropriate to perform the primary analysis on IFI by treating all-cause mortality and other events that lead to either informative censoring or missing data as failures. The review team's position is supported by the literature on combined endpoints. This reviewer refers to the paper by Lubsen[3]. These authors discuss why analyzing specific non-fatal events in isolation may lead to spurious conclusions about efficacy unless the events considered are combined with all-cause mortality with examples of trials conducted in real time.

The review team discussed the inclusion of all-cause mortality versus IFI related (caused) mortality. It has been shown in the literature that it is quite difficult to determine if a death was possibly due to an invasive fungal infection. In Kirch[4] the authors discuss the frequency of misdiagnosis despite increased diagnostic technology with infections being one of the most common errors. Sharma[5] conducted a retrospective analysis of antimortem and postmortem pulmonary findings in patients receiving blood and bone marrow transplant recipients. They found that 5 of the 11 patients with pulmonary aspergillosis (45%) at autopsy were not receiving treatment for these conditions at the time of death. Also 10 of 16 patients (63%) being treated for suspected pulmonary aspergillosis at the time of death had no evidence of pulmonary aspergillosis at autopsy.

During a discussion of other events that can lead to informative censoring, it was made clear that as part of the clinical management, subjects who are thought to potentially have a fungal infection are often empirically treated with an anti-fungal drug in addition to the study medication. While many of these patients in the two studies (C/I98-316 and P01899) were determined to have not had a proven or probable fungal infection, the empiric treatment with the anti-fungal drugs other than study medication could have suppressed an early fungal infection, or these drugs could have contributed to the prevention of a fungal infection. Therefore, the review team felt that the events such as use of anti-fungal dugs other than the study medication during the study period along with loss to follow-up should also be considered as part of the composite primary endpoint.

2. Analysis of prophylaxis for Aspergillus alone

The sponsor conducted an analysis of the event of breakthrough aspergillosis infections and determined that a significant difference was found. This analysis in essence treated all deaths without an aspergillosis infection and all breakthrough fungal infections due to other pathogens as successes. This is a concern given that treatment of these other infections could have also treated an aspergillosis infection or could have helped to prevent one. We point again to the article by Lubsen[3] who discuss why analyzing specific non-fatal events in isolation may lead to spurious conclusions about efficacy.

3. Non-inferiority design with comparators not approved for the indication sought by the applicant (namely, [redacted] infections)

Regarding the use of fluconazole as the comparator in study C/I98-316, the review team repeatedly had informed the applicant that since the comparator, fluconazole, is not approved for the broad indication proposed by the applicant, a non-inferiority analysis would not be able to support the efficacy of posaconazole for [redacted] infections and that a superiority analysis would be needed to provide evidence that posaconazole is effective for pathogens other than *Candida*. The results of this study show that there is not statistically sufficient evidence that posaconazole is superior to fluconazole in terms of clinical success. However the data do provide sufficient evidence of comparable performance of posaconazole to that of fluconazole in terms of clinical success established by means of non-inferiority with the sponsor's defined 15% margin (see the next discussion point). There is some indication that posaconazole may be effective in preventing aspergillosis due to the numerical difference in breakthrough fungal infections. However, we leave this determination to the clinical and microbiological reviewers.

Regarding the use of fluconazole and itraconazole as the comparators in study P01899, the sponsor was told that since these drugs were not approved for prophylaxis of fungal infections in this patient population, the sponsor would need to show a superior result. Given that the results do show statistically significant superiority of posaconazole, this issue is resolved in study P01899.

4. Justification for the non-inferiority margin

The sponsor proposed a 15% non-inferiority margin for the percent difference for study C/I98-316. The review team requested justification of the proposed 15% non-inferiority margin from the sponsor on 4/24/06. In the sponsor's response on 5/23/06, the sponsor agreed that the exact rate of IFI is difficult to estimate particularly in this patient population, and published rates have ranged from 5% - 40%. The sponsor referred to the study by Slavin[1] which the sponsor states demonstrated the safety and efficacy of fluconazole for preventing opportunistic infections in subjects undergoing hematopoietic stem cell transplant. However, the population and the prophylaxis strategy in the Slavin article were not identical to study C/I98-316. This article found the IFI rates were 17.6% for placebo and 6.6% for fluconazole (odds ratio of 3.3 for placebo versus fluconazole with 95% CI of [1.4, 6.5]). The sponsor then determined that a non-inferiority margin that would retain 50% of this effect would be 1.18. They argued that the selected margin based on 15% relative difference in IFI incidence with regard to fluconazole would correspond to a margin of 1.1625 for the odds ratio based on the observed number of 43 IFIs in the primary time period and this margin would retain more than 50% of the fluconazole effect.

The applicant's justification for the choice of non-inferiority margin is based on just one study that used different endpoints, different prophylaxis strategy and enrolled a different population of patients. The determination of an appropriate non-inferiority

margin is difficult in the setting of a treatment study. However, it is far more difficult in the setting of a prophylaxis indication. The literature shows superiority of fluconazole in a least one study referenced by the sponsor. The statistical team relied on the clinical team to determine if the subjects in this study are of similar risk for developing fungal infections as those in the reference study. Note that the review team has no evidence that the sponsor conducted a thorough search of all appropriate articles to determine the adequacy of their proposed non-inferiority margin. This is important because one should not ignore, and must take into account, literature (if it exists) that does not show superior efficacy of fluconazole over placebo as well.

5. Issues of concentration/response found by clinical pharmacology reviewer

The clinical pharmacology reviewer determined that there was a significant concentration response association between posaconazole levels obtained in study C/I98-316 and clinical response. The following table, reproduced from Seong Jang's analysis, shows that subjects with the lowest quartile of posaconazole concentrations had a higher failure rate than those in the upper quartiles leading one to believe that patients who are not able to obtain high enough concentrations of posaconazole may obtain poorer outcomes because of it. The clinical pharmacology review commented on the high variability of concentrations seen with posaconazole and that absorption of posaconazole is highly affected by fat.

**Table 28: Incidence of Clinical Failure in the All Treated population during the Primary Time Period in 4 quartiles of POS $C_{avg}$ (Study C98-316).**

| Quartiles | Q1 | Q2 | Q3 | Q4 |
|---|---|---|---|---|
| **$C_{avg}$ (ng/mL)** | **21.5-557** | **557-915** | **915-1563** | **1563-3650** |
| **Clinical Failure** | **44.4% (28/63)** | **20.6% (13/63)** | **17.5% (11/63)** | **17.5% (11/63)** |

However, one problem with looking at the success rates of the lowest concentration group of posaconazole is that we do not know how fluconazole would have done in patients similar to those found in this lowest concentration group. There was some discussion that the posaconazole patients with the lowest exposure could have been a more ill group of patients.

We attempted to model posaconazole plasma concentrations versus baseline risk factors to see if a model that predicted much of the low concentration seen with posaconazole could be found. This model could then be used to predict for control patients hypothetical posaconazole concentrations. Control patients could then be grouped into similar quartiles for comparison. However, we were unable to come up with an adequate model (using either actual concentrations or binary endpoint based on the quartiles).

Absent convincing evidence that baseline risk factors alone can explain the low posaconazole levels, we continue to be concerned that the low posaconazole levels may be causing, at least in part, the low success rates in these subjects.

[redacted]

We would recommend the information on this exposure-response finding be included in the label and studied further in a phase IV commitment.

Labeling

On June 20, 2006, the clinical team decided to redefine the clinical success endpoint that would be included in the drug label. Use of this redefined endpoint (not reported in this review) does not change the qualitative conclusions of the studies from the results that are reported here.

### 5.1.2 Collective Evidence

Two comparative Phase III studies were conducted using posaconazole as prophylaxis for the prevention of invasive fungal infections in high risk patients. C/I98-316 was a randomized double-blind active controlled trial of posaconazole versus fluconazole as control in HSCT recipients receiving high-dose immunosuppressive therapy for graft-versus-host disease (GVHD). Study P01899 was a randomized, open label, active controlled trial of posaconazole versus fluconazole or itraconazole as control (by center) in acute myelogenous leukemia or myelodysplastic syndrome (AML/MDS) patients with severe, prolonged neutropenia due to remission-induction chemotherapy.

The following table provides a summary of clinical success rates for the two studies (C/I98-316 and P01899). For study C/I98-316, clinical failure was defined in the protocol as the occurrence of a proven or probable IFI, receipt of more than 5 days of empiric treatment with a systemic antifungal drug other than the study drug during the Primary Time Period, or discontinuation from the Primary Time Period (i.e., subject not followed for the entire duration of the period). For study P01899, clinical failure was defined by the review team as follows: occurrence of a proven or probable IFI, receipt of 4 or more days of empiric treatment with another antifungal for suspected IFI, use of IV alternative antifungal medication for >3 consecutive days or >= 10 cumulative days, discontinuation due to an AE regardless of determination of causality, discontinuation due to treatment failure, withdrawn from the study for any reason, lost to follow-up during the oral treatment phase (oral treatment plus 7 days) or death during the oral treatment phase. Note that the review team redefined the sponsor's defined clinical failure for study P01899 since in the sponsor's analysis some patients who died were not considered failures and since the sponsor only included discontinuations due to *drug-related* adverse events in the definition of failure.

[redacted]

**Table 29: Summary of study results for C/I98-316 and P01899 (All Randomized Subjects)**

| | C/I98-316* | | P01899* | |
|---|---|---|---|---|
| | Posaconazole (N =301) | Fluconazole (N=299) | Posaconazole (N =304) | Flu/Itra (N=298) |
| | n (%) | n (%) | n (%) | n (%) |
| Clinical Success | 202 (67%) | 189 (63%) | 166 (55%) | 126 (42%) |
| Clinical Failure* | 99 (33%) | 110 (37%) | 138 (45%) | 172 (58%) |
| Due to | | | | |
| IFI | 16 | 27 | 7 | 25 |
| Death** | 58 | 59 | 18 | 26 |
| Use of Systemic Therapy | 10 | 9 | 63 | 88 |
| Not followed/discontinued | 24 | 30 | 51 | 35 |
| CI for the difference*** | (-2.7, 12.2) | | (4.3, 20.1) | |

*: Primary time point is at 16 weeks for study C/I98-316 and at end of oral therapy plus 7 days for study P01899.
**: For study C/I98-316, 10 posaconazole patients and 16 fluconazole patients were counted as both IFI and death. For study P01899, 1 posaconazole patient and 2 control patients were counted as both IFI and death. All other outcomes are ranked by order in the table.
***: 95.01% CI for study C/I98-316 and 95.13% CI for study P01899

Note that some of the concerns of the interpretations of the results of these studies include difficulty in determining an appropriate non-inferiority margin for study C/I98-316 and the open-label nature of study P01899, along with the many issue inherent with the design and analysis of prophylaxis studies. However, we believe that collectively these two studies are supportive of the efficacy of posaconazole for prophylaxis of fungal infections in these patient populations.

## 5.2 Conclusions and Recommendations

The data from the two randomized, active-controlled clinical trials submitted in this application, collectively provide sufficient evidence of comparable performance of posaconazole to that of other azoles (namely fluconazole and itraconazole) in terms of clinical success (primarily defined as invasive fungal infection free survival) by means of non-inferiority design. There is some indication that posaconazole may be effective in preventing aspergillosis infection due to the numerical difference in probable breakthrough fungal infections. However, we leave this determination to the clinical and microbiological reviewers.

# APPENDIX

The following is the sponsor's discussion of the computation of the maximum value to determine non-inferiority from the final protocol for study C/I98-316.

**Assessment of Noninferiority**

Posaconazole will be considered to be at least noninferior to fluconazole, with respect to the primary efficacy endpoint based on all treated patients, if the upper limit of the ***95.01%*** confidence interval for the adjusted odds ratio, for the effect of treatment upon the incidence of proven or probable IFI, does not exceed a maximum value corresponding to a percentage difference in ***incidence*** (with respect to the ***incidence*** of fluconazole) of 15%. The maximum value will be computed as follows:

Let

$\tilde{\pi}_{POS}$ = Posaconazole ***incidence*** to be ruled out,

$\tilde{\pi}_{FLZ}$ = Fluconazole ***incidence*** to be ruled out,

$\hat{\pi}$ = Estimated overall ***incidence*** (Total number of events/Total number of patients),

$N_{POS}$ = Number of patients in the Posaconazole treatment group,

$N_{FLZ}$ = Number of patients in the fluconazole treatment group.

Then solve the following two equations for $\tilde{\pi}_{POS}$ and $\tilde{\pi}_{FLZ}$:

$$\frac{N_{POS}\tilde{\pi}_{POS} + N_{FLZ}\tilde{\pi}_{FLZ}}{N_{POS} + N_{FLZ}} = \hat{\pi}$$

$$\frac{\tilde{\pi}_{POS} - \tilde{\pi}_{FLZ}}{\tilde{\pi}_{FLZ}} = 0.15$$

Then calculate the maximum value for the upper confidence limit of the odds ratio as:

$$\text{Maximum Value} = \frac{\tilde{\pi}_{POS}(1 - \tilde{\pi}_{FLZ})}{\tilde{\pi}_{FLZ}(1 - \tilde{\pi}_{POS})}$$

## REFERENCES

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/s/

Jyoti Zalkikar
6/22/2006 02:33:59 PM
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# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-003**

# MICROBIOLOGY REVIEW

**MICROBIOLOGY TEAM LEADER REVIEW**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** June 12, 2006

**SUBMISSION:** NDA # 22-003

**REVIEWER:** Shukal Bala, Ph.D.
Microbiology Team Leader
Division of Special Pathogen and Immunologic Drug Products
Office of Antimicrobial Products

**SUBJECT:** Posaconazole

**Introduction and Background:**
The subject of this NDA is posaconazole (SCH 56592) a triazole with activity against *Candida albicans* and *Aspergillus fumigatus*. The preclinical studies supporting the activity of posaconazole were reviewed earlier ). The clinical microbiologic studies for the prophylaxis of invasive fungal infections in high risk patients with prolonged neutropenia or who have undergone hematopoietic stem cell transplantation were reviewed by Dr Suvarna (for details see microbiology review dated May 15, 2006). This microbiology team leader review discusses essential microbiologic findings abstracted from Dr Suvarna, Dr Goodwin and Ms. Moore's reviews relevant to the labeling.

**Comments:**

1. Efficacy of posaconazole as a prophylactic agent was compared to fluconazole in studies C/I98-316 and PO1899 and itraconazole in study PO1899. Please note that
   - fluconazole is approved for the
     - treatment of oropharyngeal, esophageal and vaginal candidiasis, and
     - prophylaxis to decrease the incidence of Candidiasis in patients undergoing bone marrow transplantation; whereas
   - itraconazole is approved for the
     - treatment of Aspergillosis (pulmonary and extrapulmonary) in immunocompromised and nonimmunocompromised patients, and
     - empiric therapy in febrile neutropenic patients with suspected fungal infections

   The results of the clinical studies show lower number of breakthrough infections in patients treated with posaconazole compared to fluconazole (Tables 1 and 2) in studies C/I98-316 and P01899 and same as itraconazole (Table 2) in study P01899 during the primary treatment phase in evaluable population. Please note treatment duration varied from 1 to ≥120 days (mean: 80 days ~ posaconazole and 77 days ~

fluconazole). However, similar observations were made in all treated subjects in both the studies while patients were on therapy (Tables 3 and 4). A majority of the breakthroughs were due to *Aspergillus* or *Candida* species in patients treated with posaconazole or comparators (for details see Microbiology review by Dr Suvarna dated 5/15/06 and Medical officer review by Dr Maureen Tierney). There were fewer breakthroughs due to *Aspergillus* in patients administered posaconazole compared to fluconazole and same as subjects administered itraconazole. Overall, the numbers of breakthrough infections were small in all the groups.

Table 1: Pathogen group associated with proven (proven + probable) invasive fungal infections during the primary treatment phase (i.e., 16 weeks) in the evaluable population in randomized double-blind study C/I98-316.

| **Species** | **Posaconazole** | **Fluconazole** |
|---|---|---|
| *Aspergillus fumigatus* | 0 (0) | 2 (5) |
| *Aspergillus flavus* | 0 (0) | 2 (2) |
| *Aspergillus terreus* | 0 (0) | 0 (1) |
| *Aspergillus niger* | 0 (0) | 1 (1) |
| *Aspergillus species* | 0 (4) | 1 (8) |
| ***Aspergillus* species Total** | **0 (4)** | **6 (17)** |
| *Candida albicans* | 0 (0) | 0 (0) |
| *Candida glabrata* | 2 (2) | 1 (1) |
| *Candida krusei* | 1 (1) | 0 (0) |
| *Candida parapsilosis* | 0 (0) | 0 (0) |
| *Candida* species | 0 (0) | 0 (0) |
| ***Candida* species Total** | **3 (3)** | **1 (1)** |
| *Rhizomucor miehei* | 0 (0) | 1 (1) |
| *Pseudoallescheria boydii* | 1 (1) | 0 (0) |
| *Scedosporium prolificans* | 1 (1) | 0 (0) |
| *Trichosporon biegelii* | 1 (1) | 0 (0) |
| Other mold | 0 (0) | 1 (1) |
| **Other fungal species Total** | **3 (3)** | **2 (2)** |
| **Total** | **6 (10)** | **9 (20)** |

Table 2: Pathogen group associated with proven (proven + probable) invasive fungal infections during treatment (maximum period 12 weeks) in the evaluable populations in a randomized open label evaluator blinded study P01899

| Species | Posaconazole | Fluconazole | Itraconazole |
|---|---|---|---|
| *Aspegillus fumigatus* | 0 (0) | 0 (1) | 0 (1) |
| *Aspegillus flavus* | 0 (0) | 0 (2) | 0 (0) |
| *Aspegillus* species | 0 (2) | 1 (11) | 0 (4) |
| ***Aspergillus* species Total** | **0 (2)** | **1 (14)** | **0 (5)** |
| *Candida glabrata* | 2 (2) | 1 (1) | 0 (0) |
| *Candida krusei* + *Candida parapsilosis* | 0 (0) | 1 (1) | 0 (0) |
| *Candida tropicalis* + mold | 1 (1) | 0 (0) | 0 (0) |
| *Candida* species + mold | 0 (1) | 0 (0) | 0 (0) |
| ***Candida* species Total** | **3 (4)** | **2 (2)** | **0 (0)** |
| *Rhizomucor arrhizus* | 0 (0) | 1 (1) | 0 (0) |
| *Pseudoallescheria boydii* | 0 (0) | 1 (1) | 0 (0) |
| *Pneumocystis carinii* | 1 (1) | 0 (0) | 0 (1) |
| **Other fungal species Total** | **1 (1)** | **2 (2)** | **0 (1)** |
| **Total** | **4 (7)** | **5 (18)** | **0 (6)** |

Table 3: Pathogen group associated with proven (proven + probable) invasive fungal infections while on treatment in the all treated population in a randomized double-blind study C/I98-316.

| Species | Posaconazole | Fluconazole |
|---|---|---|
| *Aspergillus fumigatus* | 0 (0) | 3 (6) |
| *Aspergillus flavus* | 0 (0) | 2 (2) |
| *Aspergillus terreus* | 0 (0) | 0 (1) |
| *Aspergillus niger* | 0 (0) | 0 (0) |
| *Aspergillus species* | 0 (3) | 2 (8) |
| ***Aspergillus* species Total** | **0 (3)** | **7 (17)** |
| *Candida albicans* | 1 (1) | 1 (1) |
| *Candida glabrata* | 0 (0) | 1 (1) |
| *Candida krusei* | 0 (0) | 1 (1) |
| *Candida parapsilosis* | 0 (0) | 0 (0) |
| *Candida* species | 0 (0) | 0 (0) |
| ***Candida* species Total** | **1 (1)** | **3 (3)** |
| *Rhizomucor miehei* | 0 (0) | 1 (1) |
| *Pseudoallescheria boydii* | 1 (1) | 0 (0) |
| *Scedosporium prolificans* | 0 (0) | 0 (0) |
| *Trichosporon biegelii* | 1 (1) | 0 (0) |
| Other mold | 1 (1) | 1 (1) |
| **Other fungal species Total** | **3 (3)** | **2 (2)** |
| **Total** | **4 (7)** | **12 (22)** |

Table 4: Pathogen group associated with proven (proven + probable) invasive fungal infections while on treatment in all treated populations in a randomized open label evaluator blinded study P01899

| Species | Posaconazole | Fluconazole | Itraconazole |
|---|---|---|---|
| *Aspegillus fumigatus* | 0 (0) | 0 (1) | 0 (1) |
| *Aspegillus flavus* | 0 (0) | 0 (2) | 0 (0) |
| *Aspegillus* species | 0 (2) | 1 (12) | 0 (4) |
| ***Aspergillus* species Total** | **0 (2)** | **1 (15)** | **0 (5)** |
| *Candida glabrata* | 2 (2) | 1 (1) | 0 (0) |
| *Candida krusei* + *Candida parapsilosis* | 0 (0) | 1 (1) | 0 (0) |
| *Candida tropicalis* + mold | 1 (1) | 0 (0) | 0 (0) |
| *Candida* species + Mold | 0 (1) | 0 (0) | 0 (0) |
| ***Candida* species Total** | **3 (4)** | **2 (2)** | **0 (0)** |
| *Rhizomucor arrhizus* | 0 (0) | 1 (1) | 0 (0) |
| *Pseudoallescheria boydii* | 0 (0) | 1 (1) | 0 (0) |
| *Pneumocystis carinii* | 1 (1) | 0 (0) | 0 (1) |
| **Other fungal species Total** | **1 (1)** | **2 (2)** | **0 (1)** |
| **Total** | **4 (7)** | **5 (19)** | **0 (6)** |

Similar observations were made at the follow up visits in both studies C/I98-316 and P01899 (Tables 5 and 6), however the numbers were very small.

Table 5: Pathogen group associated with proven (proven + probable) invasive fungal infections during the post-treatment (follow-up) phase in the evaluable population in randomized double-blind study C/I98-316.

| Species | Posaconazole | Fluconazole |
|---|---|---|
| *A fumigatus* | 0 (0) | 1 (4) |
| *Aspergillus* species | 0 (2) | 1 (4) |
| ***Aspergillus* species Total** | **0 (2)** | **2 (8)** |
| *Candida* species | 0 (0) | 1 (1) |
| Mold | 0 (0) | 0 (1) |
| **Total** | **0 (2)** | **3 (10)** |

Table 6: Pathogen group associated with proven (proven + probable) invasive fungal infections during the post-treatment (follow-up) phase in the evaluable population in randomized double-blind study P01899.

| Species | Posaconazole | Fluconazole | Itraconazole |
|---|---|---|---|
| *A flavus* | 0 (0) | 1 (1) | 0 (0) |
| *Aspergillus* species | 0 (1) | 0 (1) | 1 (1) |
| ***Aspergillus* species Total** | **0 (1)** | **1 (2)** | **1 (1)** |
| *Kluyeromyces maxianus* | 1 (1) | 0 (0) | 0 (0) |
| **Total** | **1 (2)** | **1 (2)** | **1 (1)** |

2. Based on Medical Officer's review of oropharyngeal candidiasis (OPC) indication posaconazole appears to be active against *C. albicans* (for details see review by Dr Regina Alivistos). The Microbiology review of the clinical studies in support of OPC indication is presently under review.

2 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

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*Withheld Track Number: Microbiology-_____*

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MICROBIOLOGIST

Renata Albrecht
6/21/2006 06:54:41 PM
MEDICAL OFFICER

[redacted]

# MICROBIOLOGY REVIEW
## DIVISION OF SPECIAL PATHOGEN AND TRANSPLANT PRODUCTS

**NDA #:** 22-003

**REVIEWER:** Kalavati Suvarna
**CORRESPONDENCE DATE:** 12-21-05, 02-22-06, 03-01-06, 03-17-06
**CDER RECEIPT DATE:** 01-04-05, 02-22-06, 03-01-06, 03-17-06
**REVIEW ASSIGN DATE:** 01-04-05, 02-22-06, 03-02-06, 03-18-06
**REVIEW COMPLETE DATE:** 05-15-06

**SPONSOR:** Schering Corporation
2000 Galloping Hill Road,
Kenilworth, NJ 07033.

**SUBMISSION REVIEWED:** N-000 (original, BI, BM)

**DRUG CATEGORY:** Antifungal

**INDICATION:** Prophylaxis of invasive fungal infections

**DOSAGE FORM:** Oral Suspension

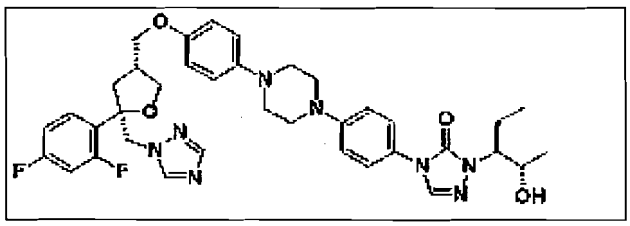
**PRODUCT NAMES:**

a. **PROPRIETARY:** Noxafil

b. **NONPROPRIETARY:** Posaconazole, SCH 56592.

c. **CHEMICAL:** 2,5-Anhydro-1,3,4 -trideoxy-2-C- (2,4-difluorophenyl) - 4 -[[4 -[4 -[4 -[1[(1S, 2S)-1-ethyl-2-hydroxypropyl] -1,5-dihydro-5-oxo-4*H*-1,2,4-triazole-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(*1H*-1,2,4-triazol-1-yl)-D-*threo*-pentitol

**STRUCTURAL FORMULA:**



Molecular weight: 700.78
Empirical Formula: $C_{37}H_{42}F_2N_8O_4$

**SUPPORTING DOCUMENTS:** IND 51,662; [redacted]

**TABLE OF CONTENTS**

## 1. EXECUTIVE SUMMARY

The sponsor is seeking approval of posaconazole (POS) oral suspension for the prophylaxis of invasive fungal infections (IFIs) in high-risk patients (≥ 13 years of age) with prolonged neutropenia or who have undergone hematopoietic stem cell transplantation. The sponsor has proposed a dose of 600 mg/day POS orally for the prophylaxis of IFIs. The duration of therapy will be based on recovery from neutropenia or immunosuppression.

***Mechanism of action:***
POS is a triazole anti-fungal compound that is chemically similar to the currently marketed triazole compounds fluconazole (FLZ), itraconazole (ITZ), and voriconazole (VRZ). The mechanism of action of POS against zygomycetes was examined in a study included in this submission and against *Candida* and *Aspergillus* species in the previous submission reviewed by Dr. Goodwin and Ms. Lynn Steele-Moore. The mechanism of action of POS is similar to other azoles in that it inhibits the lanosterol 14 α-demethylase enzyme (CYP51) involved in ergosterol biosynthesis.

***Activity in vitro:***
The *in vitro* activity of POS was measured against various fungal species according to the Clinical and Laboratory Standards Institute (CLSI) recommended methods (M27A2 and M38A). The *in vitro* activity of POS against yeasts and mold included in this submission were similar to that observed in studies reviewed previously [redacted]

***Activity in vivo:***

[redacted]

***Drug resistance:***

***Candida albicans:***
In drug resistance studies reviewed earlier by Dr. Goodwin and Ms Lynn Steele-Moore, prolonged exposure of *C. albicans* strain C43 to posaconazole did not alter the MICs following serial passages *in vitro*. Conversely, exposure of *C. albicans* to fluconazole resulted in changes to the fluconazole susceptibility indicated by the 16-60 fold rise in MICs in 5 of the 6 cultures. Please note that the clinical significance of these observations is not known.

In this submission, the mechanism of resistance to POS was characterized in two *Candida albicans* isolates with reduced susceptibility to azoles including POS. The mechanism of azole resistance in these isolates was due to mutations in the *ERG3* gene resulting in the inactivation of sterol $\Delta^{5,6}$-desaturase enzyme.

In the clinical trial C/I98-316 conducted to evaluate the safety and efficacy of POS in the prophylaxis of invasive fungal infections, oral swish cultures were performed to study fungal colonization. *C. albicans* and *C. glabrata* isolates with reduced *in vitro* susceptibility (≥ 4 fold increase in MIC) to POS and other azoles were obtained after azole prophylaxis.

***Aspergillus fumigatus:***
The sponsor has stated that spontaneous *A. fumigatus* laboratory mutants exhibiting a decrease in susceptibility to posaconazole arose at frequencies of 1 in $10^8$. The raw data supporting fluctuation in mutation frequency were not included for review. The laboratory mutants (POS MIC 1 to >8 µg/ml) were cross-resistant to itraconazole (MIC >16 µg/ml) and contained single amino acid substitution in the *CYP51A* gene. The clinical relevance of this finding is not known.

For a summary of *in vitro* studies evaluating cross-resistance between posaconazole and other azoles,

***Drug combination:***
A combination of posaconazole and amphotericin B or caspofungin was found to exhibit variable activity (antagonism, indifferent, additive or synergistic) against *A. fumigatus*, *A. flavus* and *C. albicans in vitro* and *in vivo*. In the absence of clinical relevance, the usefulness of including information on variable actvity of drug combinations against *Aspergillus* and *Candida* in the label is not known.

***Clinical microbiology:***
Two studies (C/I98-316 and P01899) were included in this submission to support the prophylaxis indication. The IFI status in these studies was characterized using the EORTC - MSG standardized definitions. For proven infections, the microbiology criteria included positive culture from blood or a sterile site or histopathological evidence of hyphae from needle aspirations or biopsy samples. For probable infections, the microbiological criteria included positive culture from sites that may be colonized [for example, sputum, bronchoalveolar lavage (BAL), sinus aspirate] or positive result for *Aspergillus* antigen in specimens of BAL, CSF, or ≥ 2 serum samples. Please note that the *Aspergillus* antigen testing was performed using *Aspergillus* antigen kit which is FDA approved for use in conjunction with other procedures such as microbiological culture or histological and radiological assessments using serum samples only. The cut-off for a positive test (an OD index of ≥ 0.5) using the FDA approved kit is lower that that used in European countries previously (OD cut-off for positive test ≥ 1.5). The lower cut-off has been stated to improve sensitivity with minimum effect on specificity. However, a recent study showed that the accuracy of the test improved with a higher threshold. It should be noted that the approved *Aspergillus* antigen test is not truly diagnostic but provides information on probability of IFIs. Positive results should be interpreted in conjunction with clinical and radiological findings as false-positive results due to presence of fungi other than *Aspergillus,* galactomannan from food, contamination from laboratory sources or administration of β-lactams are known to occur. Repeat testing of positive samples and testing of sequential serum samples for *Aspergillus* antigen is recommended by the manufacturer of the antigen detection kit. In addition to fungal culture and *Aspergillus* antigen detection, PCR testing using blood samples and *in vitro* susceptibility testing of breakthrough isolates and oral colonizers using CLSI recommended methods were performed in a central laboratory. The PCR testing was only performed for exploratory purposes and not used for diagnosis of fungal infection or fungal speciation. No correlation was observed between the PCR results and presence of galactomannan antigen or development of IFIs in the clinical studies.

In study C/I98-316, there were 20 FLZ treated patients and 10 POS treated patients who developed proven or probable IFIs during the primary treatment period (i.e., 16 weeks) in the evaluable population. In 9 patients (FLZ, n = 5; POS, n = 4) with probable infection, the diagnosis was made using *Aspergillus* antigen test. In 3 of the 9 patients, the diagnosis was based on a single test result using serum or BAL. As discussed previously, positive results should be interpreted in conjunction with clinical and radiological findings. Invasive fungal infections due to *Aspergillus* species (n = 17), *C. glabrata* (n = 1), *Rhizopus miehei* (n = 1) or unidentified mold were identified between 2 to 93 days after starting fluconazole prophylaxis. Similarly, invasive fungal infections due to *Aspergillus* species (n = 4), *C. glabrata* (n = 2), *C. krusei* (n = 1), *Pseudoallescheria boydii* (n = 1), *Scedosporium prolificans* (n = 1), *Trichosporon biegelii* (n = 1) were identified between 9 and 105 days after starting posaconazole prophylaxis. Limited *in vitro* susceptibility testing was performed on breakthrough isolates using CLSI recommended methods. The POS MICs against *Aspergillus* (n = 3) and *Candida* (n = 1) isolates were $\leq$ 0.125 µg/ml while against 1 *Scedosporium* isolate, the POS MIC was 8 µg/ml.

In study P01899, 18 FLZ treated patients developed proven or probable IFIs during the oral treatment phase in the evaluable population. The majority of invasive fungal infections were due to *Aspergillus* species, *A. fumigatus* or *A. flavus* (n = 14). The remaining infections were due to *Candida* species other than *C. albicans* (n = 2), *Rhizopus arrhizus* (n = 1) or *Pseudoallescheria boydii* (n = 1). The IFIs were identified within 5 to 81 days of FLZ prophylaxis. There were 7 POS treated patients who developed proven or probable invasive fungal infections. The invasive fungal infections were due to *Aspergillus* species (n = 2), *C. glabrata* (n = 2), or mixed infections due to *Candida* species and mold (n = 2). One patient had infection due to *Pneumocystis carinii*. The invasive infections were identified on either the first day of treatment or 53 days after starting POS prophylaxis. None of the patients receiving ITZ prophylaxis developed a proven fungal infection during treatment. Six patients were identified as having probable fungal infections. Of the 6 patients, 4 had infections due to *Aspergillus* species, 1 due to *A. fumigatus* and 1 due to *Pneumocystis carinii*. Probable infections were diagnosed using the *Aspergillus* antigen test in 15 subjects (FLZ, n = 9; POS, n = 2; ITZ, n = 4). Few subjects had only one serum sample that was positive. As discussed previously, the results of the *Aspergillus* antigen test should be interpreted in conjunction with clinical and radiological findings. The baseline *in vitro* susceptibility testing was performed for 6 isolates (4 *Aspergillus* isolates and 2 *Candida* isolates). The POS MICs for all 6 isolates were $\leq$ 0.125 µg/ml.

Overall, the numbers of proven and probable breakthrough fungal infection were higher in FLZ and ITZ arms compared to the POS arm. Based on data from these two studies, posaconazole has the potential to prevent invasive fungal infections.

## 2. INTRODUCTION AND BACKGROUND

The subject of this NDA is posaconazole (POS), an azole antifungal agent for the prophylaxis of invasive fungal infections (IFIs) in high-risk patients (≥ 13 years of age) with prolonged neutropenia or who have undergone hematopoietic stem cell transplantation. The sponsor has proposed a dose of 600 mg/day POS orally (as divided doses with meals) for the prophylaxis of IFIs. The duration of therapy will be based on recovery from neutropenia or immunosuppression.

POS is a triazole anti-fungal compound. It belongs to the azole class of drugs which includes the currently marketed compounds fluconazole (FLZ), itraconazole (ITZ), and voriconazole (VRZ). In humans, the mean half-life of POS is 34.7 hours after administration of 400 mg oral suspension twice a day. POS is highly protein bound (97 to 99 %). A 2.6 to 4-fold increase in the relative bioavailability of POS is observed when a single dose of 400 mg POS is given with nonfat or high fat meal compared to fasting condition. In patients with refractory fungal infections, the mean area under the plasma concentration versus time curve (mean AUC) for POS is a third (8.6 µg.hr/ml) of that observed in healthy volunteers (29.5 µg.hr/ml). The mean maximum plasma drug concentration (mean $C_{max}$) for POS in healthy volunteers and patients is 2.9 and 0.9 µg/ml, respectively.

## 3. PRECLINICAL MICROBIOLOGY

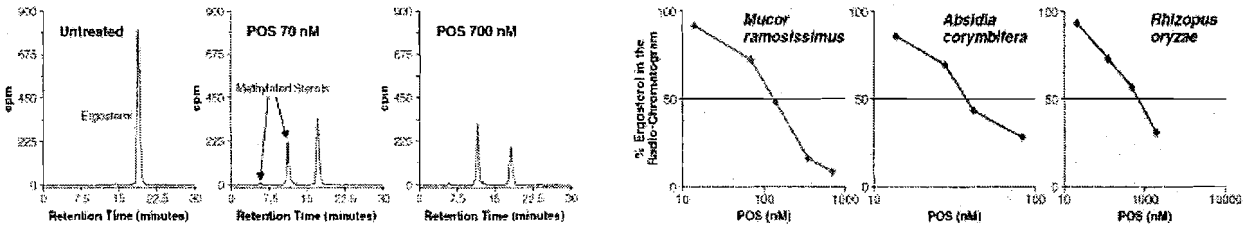
For the preclinical microbiology information (mechanism of action, activity *in vitro* and *in vivo,* drug resistance, cross-resistance, and drug combinations) reviewed previously,

In this submission, the sponsor included some additional information in support of the mechanism of action, activity *in vitro,* and mechanism of resistance.

**Mechanism of action:**
The effect of posaconazole on sterol biosynthesis was examined in zygomycetes (study report D48627). The strains of *Absidia*, *Rhizopus* and *Rhizomucor* were labeled with [$^{14}$C]-acetate in the presence or absence of drug. The sterols were extracted and resolved by high performance liquid chromatography. The sterol peaks in the test samples were identified using gas chromatography and mass spectroscopy. Squalene, lanosterol, and ergosterol were used as standards. The relative amount of ergosterol in the sterol fraction was calculated by measuring the area of the peak corresponding to [$^{14}$C]-labeled ergosterol and expressing the value as a percentage of the total area in the radio-chromatogram. The amount of drug required to reduce the ergosterol peak by 50% ($IC_{50}$) was calculated. Exposure of *Absidia*, *Rhizopus* and *Rhizomucor* cells to posaconazole results in decrease of the ergosterol peak and increase in other peaks labeled as methylated sterols (Figure 1). The inhibition of ergosterol synthesis was dependent on POS concentration. Please note that the chromatogram showing peak elution times for the standards were not shown for comparison. The findings in this study and those reported earlier show that POS inhibits the synthesis of ergosterol in *Candida* species, *Aspergillus* species, and Zygomycetes.

Figure 1: Effect of posaconazole on sterol biosynthesis.

*Mucor ramosissimus*




**Activity *in vitro*:**

In studies reviewed previously [redacted], *in vitro* activity of POS was measured against various fungal species according to the Clinical and Laboratory Standards Institute (CLSI) recommended methods [redacted]. *In vitro* activity was tested against 2,870 isolates of different *Aspergillus* spp., including *A. fumigatus, A. flavus, A. niger* and *A. terreus* ($MIC_{90} \leq 1.0$ µg/ml), 208 isolates of *Fusarium* spp. ($MIC_{90}$ 2 - 128 µg/ml), 50 isolates of *Coccidioides* spp ($MIC_{90}$ 1 µg/ml), 257 Zygomycetes ($MIC_{90}$ 0.25 - 16 µg/ml), 7370 isolates of *Candida albicans* ($MIC_{90}$ 0.063 µg/ml), 81 to 2106 isolates of *Candida* spp. other than *C. albicans* ($MIC_{90}$ 0.25 - 2 µg/ml), and 1219 *Cryptococcus* spp ($MIC_{90}$ 0.25 µg/ml) isolates. The *in vitro* activity of posaconazole against yeasts and mold included in this submission was similar to that observed in studies reviewed previously. Please note that the correlation between MIC and treatment outcome has not been established.

**Drug Resistance:**

The mechanism of resistance in two *C. albicans* clinical isolates (C410 and C655) with an MIC of > 8 µg/ml to various azoles was examined (study report D46055). Mutations in the *ERG11* (lanosterol 14α-demethylase) and *ERG3* ($\Delta^{5,6}$–sterol desaturase) genes were determined by sequencing. Additionally, the sterols produced by these isolates were analyzed. An azole susceptible *C. albicans* isolate (C43) was used as control. The minimum inhibitory concentrations (MICs) of different azoles against the 3 isolates measured using the CLSI method M27-A is shown in Table 1. For isolate C410, no missense mutations were observed in the *ERG11* gene. For isolate C655, mutation in *ERG11* gene resulting in substitution of aspartic acid (D) at position 116 to glutamic acid (E) was observed. This mutation is also seen in azole susceptible isolate C43. Mutations resulting in introduction of a stop codon were observed in the *ERG3* gene of both C410 and C655 isolates but not in C43 isolate. The inactivation of sterol $\Delta^{5,6}$-desaturase enzyme encoded by *ERG3* gene can prevent accumulation of methylated sterols and cause azole resistance. The major sterol identified in these isolates was stated to be ergosta-7, 22-dien-3-ol, an ergosterol precursor. However, data from the sterol analysis were not shown.

Table 1: The minimum inhibitory concentrations (MICs) of different azoles against *C. albicans* isolates

| Organism | SPRI Strain # | MIC (µg/mL) | | | | |
|---|---|---|---|---|---|---|
| | | POS | ITZ | FLZ | VOR | AMB |
| *C. albicans* | C43 | 0.03 | 0.006 | 0.125 | 0.03 | 0.5 |
| *C. albicans* | C665 | >8 | >8 | >256 | >16 | 2 |
| *C. albicans* | C410 | >8 | >8 | 256 | >16 | 4 |

## 4. CLINICAL MICROBIOLOGY

Two clinical studies (C/I98-316 and P01899) were included in this submission to support the prophylaxis indication. These studies are discussed in the following sections.

### 4.1. Study C/I98-316

This was a Phase 3, randomized, multi-center, double-blind, active control, parallel group, comparative study of POS versus FLZ in the prophylaxis of IFIs in high-risk subjects with graft versus host disease (GVHD) following allogeneic stem cell transplantation. Approximately 600 subjects from United States, Argentina, Australia, Austria, Brazil, Canada, The Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Mexico, The Netherlands, Peru, Poland, Portugal, Singapore, Saudi Arabia, South Africa, Spain, Sweden, and United Kingdom were enrolled. Protocol-eligible subjects were randomized to receive either 600 mg POS (200 mg TID), or 400 mg FLZ QD for 16 weeks or until an IFI occurred. Subjects with a history of proven or probable mold infection requiring secondary prophylaxis were excluded from study.

The primary efficacy endpoint of the study was the incidence of proven or probable IFIs within 16 weeks (112 days) of the first dose of treatment or 112 days from randomization if study drug was never taken (primary time period). For the purpose of this review, only treated patients were analyzed. Please note that the treatment duration varied from 1 to ≥ 120 days (mean duration in days = 80 for POS; 77 for FLZ). A clinical failure was defined as either the presence of a proven or probable IFI, or more than 5 days of empiric treatment with a systemic antifungal other than assigned study drug. Subjects not followed for the entire 16-week treatment phase were also considered as failures.

All subjects were followed one and two months after the 16-week treatment phase, including those subjects who developed an IFI during treatment. Subjects had periodic evaluations for the presence of fungal infection. These evaluations included signs and symptoms of infection, a physical examination, chest x-ray, chest CT scan, fungal cultures using blood, bronchoalveolar lavage (BAL), sputum, pleural fluid, or biopsy samples, if clinically indicated. Serial *Aspergillus* antigen testing and fungal PCR were also performed at a central laboratory.

*Aspergillus* antigen testing was performed by Dr. Paul Verweii (Netherlands) using serum, CSF, and BAL fluid. Circulating *Aspergillus* galactomannan was detected using *Aspergillus* enzyme immunoassay [redacted]. Literature reports suggest that the threshold for a positive test using this kit was an optical density (OD) index of ≥ 1.5 while that of the FDA approved kit manufactured by [redacted] was ≥ 0.5. Upon query regarding the differences in the two kits, the sponsor stated that [redacted] acquired [redacted] in 1999 and the two kits were the same. The kit is currently marketed as [redacted] *Aspergillus* antigen kit. Please note that the test kit manufactured by [redacted] is approved in the US for detection of antigen in serum samples only. The OD index cut-off for a positive test is ≥ 0.5. The European Organization for Research and Treatment of Cancer (EUORTC), Invasive Fungal Infections Cooperative Group, and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG), have proposed galactomannan antigen positivity as a diagnostic criterion for invasive aspergillosis. Although galactomannan antigen detection test is FDA approved for the diagnosis of invasive aspergillosis, false positive reactions have been reported due to translocation of galactomannan antigen in food (Gangneux *et al.*, Lancet 2002,

359:1251) and in patients receiving piperacillin/tazobactom (Adam *et al.,* Clin. Infect. Dis., 2004, 38: 917-920). Additionally, cross-reactivity due to presence of other fungi such as *Penicillium* species, *Rhodotorula* and *Paecilomyces* has been observed (Swanink *et al.,* Clin. Microbiol., 1997, 35:257-260). The usefulness of the assay for measuring drug efficacy is not known. The aspergillus antigen test results from the clinical studies were considered positive if the OD index was $\geq$ 0.5 despite the fact that these were multi-center trials and there were differences in European and US cut-off values for positive tests.

Fungal PCR was performed by Dr. Holger (Germany) using blood samples. Fungal PCR is an experimental method. It has not been integrated into the consensus EORTC/MSG criteria for diagnosis of probable/possible IFIs. The PCR data collected in these studies was not used for speciation of fungal isolates or adjudication of IFIs. Fungal DNA was extracted from patient's blood samples. The conserved region of the 18s rRNA gene of fungi was amplified by PCR. The PCR product was hybridized with the biotin labelled *Aspergillus fumigatus* or *Candida* spp. oligonucleotides and detected using an ELISA assay. The DSM-Strains (German Collection of microorganisms) of the medically important fungal species of *Aspergillus* (*A. fumigatus, A. flavus, A. niger, A. terreus, A. versicolor)* and *Candida* (*C. albicans, C. tropicalis, C. glabrata, C. krusei, C. parapsilosis*) were used as positive controls. The negative controls were not specified. A published report from Dr. Holger's laboratory reported a sensitivity of 100% (95% confidence interval [CI], 48 – 100%) and a specificity of 65% (95% CI, 53 – 75%) for the PCR assay in stem cell transplant patients.

Fungal susceptibility testing was done in four laboratories according to the region. However, all samples were retested in Dr. Rinaldi Laboratory (University of Texas, San Antonio). Susceptibility testing was performed according to the Clinical Laboratory Standards Institute (CLSI, previously known as National Committee for Clinical Laboratory Standards) methods. For the purpose of this review, susceptibility data collected in the central laboratory were used for analysis.

As mentioned above FDA analysis was performed on all treated patients. The modified intent-to-treat (MITT) and the evaluable subsets were also analyzed. The MITT subset was defined as subjects receiving at least one dose of study drug (capsules or suspension) and who met protocol specified criteria for acute/chronic GVHD at baseline or have sufficient levels of iatrogenic immunosuppression to consider them high-risk for IFI. The evaluable subset was defined as subjects from the MITT subset who met the entry criteria, received at least 80% of the assigned treatment based on the actual treatment duration, and did not receive concomitant medications or therapies that would confound the analysis of efficacy during the treatment phase. Figure 2 depicts the various study periods. Analysis was performed on the primary time period (i.e., 16 weeks) and post-treatment phase.

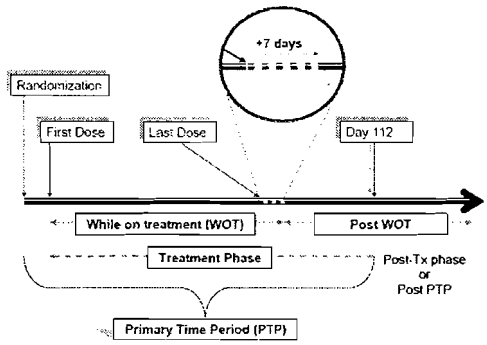



Figure 2: Study Period Diagram

The number of patients randomized to the study and numbers in the different populations are shown in Table 2.

Table 2: The number of patients in each analysis population.

| Populations (n) | Fluconazole Arm (n) | Posaconazole Arm (n) |
|---|---|---|
| All randomized (599) | 298 | 301 |
| All treated (579) | 288 | 291 |
| MITT (445) | 234 | 211 |
| Evaluable (384) | 204 | 180 |

N = number of subjects

All subjects who were considered treatment failures (according to the investigator or the protocol definition of >5 days of systemic antifungal use) or who were classified by the investigator as having possible, probable, or proven IFI were referred to the Data Review Committee (DRC) for adjudication. The panel reviewed patient profiles (consisting of clinical, microbiological, and radiological data in the database) and narrative summaries (summarizing the chronology of the events, risk factors for IFI, diagnostic tests, and treatments captured in various modules of the clinical database) in order to characterize the IFI status using the EORTC - MSG standardized definitions (Tables 3 and 4).



Table 3: EORTC - MSG standardized definitions for invasive fungal infections

**EORTC[a] – MSG[b] FUNGAL CRITERIA[c] (SEPTEMBER 1998)**

**PROVEN INVASIVE FUNGAL INFECTIONS**

**DEEP TISSUE INFECTIONS**

| MOULDS[d] | YEASTS[d] |
|---|---|
| Histo/cytopathology showing hyphae or spherule (filamentous fungi without yeast forms) from a needle aspiration or biopsy with evidence of associated tissue damage (either microscopically or unequivocally by imaging). | Histo/cytopathology showing yeast cells and/or pseudohyphae from a needle aspiration or biopsy excluding mucous membranes |
| OR | OR |
| Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection. | Positive culture obtained from a normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine, sinuses and mucous membranes by a sterile procedure. |
| | OR |
| | Microscopy (India Ink, mucicarmine stain) or antigen positivity for cryptococcus in CSF |

**FUNGEMIA**

| MOULDS[d] | YEASTS[d] |
|---|---|
| Positive blood culture of fungi excluding *Aspergillus spp.* and *Penicillium spp.* other than *P. marneffei*, accompanied by temporally related clinical signs and symptoms compatible with the relevant organism | Positive percutaneous blood culture of *Candida* and other yeasts in patients with temporally related clinical signs and symptoms compatible with the relevant organism. |

**ENDEMIC FUNGAL INFECTIONS** (histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis)

Either systemic or only confined to lungs, must be proven by culture from the site affected, in a host with symptoms attributed to the fungal infection. If cultures are negative or unattainable, histopathological demonstration of the appropriate morphological forms must be combined with serological support.

**PROBABLE INVASIVE FUNGAL INFECTIONS**

Defined as at least one criterion from host sector
**AND**
one microbiological criterion
**AND**
one major (or two minor) clinical criteria from an abnormal site consistent with infection.

**POSSIBLE[e] INVASIVE FUNGAL INFECTIONS**

Defined as at least one criterion from host sector
**AND**
one microbiological **OR** one major (or two minor) clinical criteria from an abnormal site consistent with infection.

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[a] EORTC = European Organization for Research and Treatment of Cancer.

[b] Mycosis Study Group.

[c] Criteria have not yet been formally approved by the EORTC and MSG.

[d] Append identification at genus or species level if available.

[e] The **POSSIBLE CATEGORY** is NOT recommended for use in clinical trials on antifungal agents, but for use in studies on empirical treatment, epidemiological studies and studies on health economics when needed.

Table 4: Host factors, microbiological and clinical criteria for probable and possible invasive fungal infections.

**CRITERIA FOR PROBABLE AND POSSIBLE INVASIVE FUNGAL INFECTIONS**

**Host Factors**

1. Neutropenia: PMN<500/mm$^3$ for more than 10 days.
2. Persistent fever for >96 hours refractory to appropriate broad spectrum antibacterial treatment.
3. Body temperature either >38°C or <36°C AND any of the following predisposing conditions:
   a. Prolonged neutropenia (>10 days) in the previous 60 days.
   b. Recent or current use of significant immunosuppressive agents in the previous 30 days.
   c. Invasive fungal infection in a previous episode.
   d. Co-existence of AIDS
4. Signs and symptoms indicating GVHD
5. Prolonged use of corticosteroids (>3 weeks).

**Microbiological Criteria**

1. Positive culture of a mould (including *Aspergillus* spp, *Fusarium* spp, Zygomycetes, *Scedosporium* spp), *C. neoformans* from sputum, BAL.
2. Positive culture or cytology/direct microscopy for moulds from sinus aspirate.
3. Positive cytology/direct microscopy for a mould or *Cryptococcus* from sputum, BAL.
4. Positive aspergillus antigen in BAL, CSF or ≥2 blood samples.
5. Positive cryptococcal antigen in blood
6. Positive cytology/direct microscopy for fungal elements other than *Cryptococcus* in sterile body fluids.
7. Two positive urine cultures of yeasts in the absence of urinary catheter.
8. Candida casts in urine in the absence of urinary catheter
9. Positive blood culture of *Candida* spp.
10. Pulmonary abnormality and negative bacterial cultures of any possible bacteria from any specimen related to the lower respiratory tract infection including blood, sputum, BAL, etc.

**CRITERIA FOR PROBABLE AND POSSIBLE INVASIVE FUNGAL INFECTIONS**

**Clinical Criteria**

Should be related to the site of microbiological criteria and temporally related to current episode.

| MAJOR | MINOR |
|---|---|
| **Lower Respiratory System Infection** | |
| Any of the following: new infiltrate on CT imaging; halo sign, air-crescent sign or cavity within an area of consolidation. | 1. Symptoms of LRTI (cough, chest pain, hemoptysis, dyspnea)<br>2. Physical findings of pleural rub<br>3. Any new infiltrate not fulfilling major criterion |
| **Sinonasal Infection** | |
| Suggestive radiological evidence of invasive infection in the sinuses (i.e. erosion of sinus walls or extension of infection to neighboring structures, extensive skull base destruction). | 1. Upper respiratory symptoms (nasal discharge, stuffiness, etc.)<br>2. Nose ulceration or eschar of nasal mucosa or epistaxis<br>3. Periorbital swelling<br>4. Maxillary tenderness<br>5. Black necrotic lesions or perforation of the hard palate |
| **Central Nervous System Infection** | |
| Suggestive radiological evidence of CNS infection (i.e. meningitis extending from a perinasal, auricular or vertebral processes; intracerebral abscesses or infarcts) | (CSF negative for other pathogens by culture, microscopy and malignant cells)<br>1. Focal neurological symptoms and signs (including focal seizures, hemiparesis and cranial nerve palsies)<br>2. Mental changes<br>3. Meningeal irritation findings<br>4. Abnormalities in CSF biochemistry and cell count |
| **Disseminated Fungal Infection** | |
| 1. Papular or nodular skin lesions without any other explanation.<br>2. Intraocular findings suggestive of hematogenous fungal chorioretinitis or endophthalmitis. | |
| **Chronic Disseminated Candidiasis** | |
| Small, peripheral, target-like abscesses (Bull's eye) in liver and/or spleen demonstrated by CT, MRI or USS. | |
| **Probable Candidemia** | |
| No prominent signs or symptoms of infection in patients with positive blood culture of *Candida*. | |

The number of subjects with proven, probable, and possible invasive fungal infections in the different populations during the primary time period (i.e., end of 16 weeks) is shown in Table 5. As the primary endpoint of the study was incidence of proven or probable fungal infections at 16 weeks, only these infections are discussed in the following sections. In the evaluable populations, 20 FLZ treated patients developed proven or probable IFIs compared to 10 in the POS arm (Table 5). The results of *Aspergillus* antigen and PCR testing are shown in Table 6. As mentioned previously an OD index of $\geq$ 0.5 was considered as positive for aspergillus antigen. The antigen testing was done using serum samples for all patients except one patient where BAL fluid was tested. Five patients in the FLZ arm and 4 patients in the POS arm were considered to have probable infection based on *Aspergillus* antigen tests and clinical/radiological findings. It should be noted that 1 of 5 FLZ treated patients and 1 of 4 POS treated patients with probable infections had only one serum sample positive for aspergillus antigen (shaded rows, Table 6). In one POS treated patient, the aspergillus antigen test was positive using a single BAL sample (shown as bold, Table 6). According to the protocol, the microbiology criterion for probable IFIs is fulfilled if the aspergillus antigen test is positive using $\geq$ 2 serum samples or a single BAL/CSF sample. However, false-positive results have been known to occur due to inadequate sample storage, contaminating galactomannan from food or laboratory, administration of β-lactams, and other cross-reactive epitopes. Additionally, there are controversies regarding the correct threshold for a positive test as the accuracy of the test improves with a higher threshold (Rex, 2006, CID 42: 1428-1430; Pfeiffer *et al.*, 2006, CID 42: 1417-1427). Therefore, the results

of the antigen tests should be interpreted with caution and only in conjunction with other diagnostic procedures such as microbiological culture or evidence from histological and radiological examinations. The PCR test was not used for diagnosis of fungal infections but for exploratory purposes. The results in Table 6 show that there was no correlation between a positive PCR result and occurrence of invasive fungal infections or positive culture.

In the fluconazole arm, the proven or probable invasive fungal infections were due to *Aspergillus* species (n = 17), *C. glabrata* (n = 1), *Rhizopus miehei* (n = 1) or unidentified mold (Tables 6 and 7). Invasive infections due to these pathogens were identified within 2 to 93 days after starting fluconazole prophylaxis (Table 6). In the posaconazole arm, the invasive fungal infections were due to *Aspergillus* species (n = 4), *C. glabrata* (n = 2), *C. krusei* (n = 1), *Pseudoallescheria boydii* (n = 1), *Scedosporium prolificans* (n = 1), and *Trichosporon biegelii* (n = 1). The invasive infections were identified between 9 and 105 days after starting posaconazole prophylaxis (Tables 6 and 7).

Limited *in vitro* susceptibility testing was performed on breakthrough isolates. For the purposes of this review, minimum inhibitory concentrations (MICs) reported by the central laboratory were used for analysis. The POS MICs against 3 *Aspergillus* isolates and 1 *Candida* isolate were $\leq$ 0.125 µg/ml. The POS MIC against 1 *Scedosporium* isolate was 8 µg/ml.

Table 5: The number of patients who developed proven, probable, or possible invasive fungal infections during primary time period (i.e. 16 weeks) in the different populations

| ***All randomized*** | | |
|---|---|---|
| **IFIs** | **Fluconazole (n =298)** | **Posaconazole (n = 301)** |
| *Proven* | 13 | 11 |
| *Probable* | 14 | 5 |
| *Possible* | 25 | 11 |
| ***Treated*** | | |
| **IFIs** | **Fluconazole (n = 288)** | **Posaconazole (n = 291)** |
| *Proven* | 13 | 10 |
| *Probable* | 14 | 5 |
| *Possible* | 25 | 11 |
| ***MITT*** | | |
| **IFIs** | **Fluconazole (n = 234)** | **Posaconazole (n = 211)** |
| *Proven* | 12 | 9 |
| *Probable* | 12 | 4 |
| *Possible* | 19 | 9 |
| ***Evaluable*** | | |
| **IFIs** | **Fluconazole (n = 204)** | **Posaconazole (n = 180)** |
| *Proven* | 9 | 6 |
| *Probable* | 11 | 4 |
| *Possible* | 18 | 7 |

IFIs = invasive fungal infections.

Table 6: Pathogen identified as cause of invasive fungal infection during the primary treatment phase with fluconazole or posaconazole.

| SubID | Treated | MITT | Evaluable | Pathogen (source**) | IFI | Treatment duration | Day of onset of IFI after first dose | MIC (µg/ml)[$] | Aspergillus antigen result (day of result)[@] | PCR result (day of result) |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Fluconazole*** | | | | | | | | | | |
| C012000006 | yes | yes | yes | *Aspergillus flavus* (BAL fluid) | Proven | 85 | 85 | ND | Negative | Negative |
| C015000130 | yes | yes | yes | *Aspergillus fumigatus* (Sputum) | Proven | 115 | 93 | ND | 1 Positive (115) | Asp (50; 76; 100) |
| C016000083 | yes | yes | yes | *Aspergillus niger* (Sphenoid sinus) | Proven | 20 | 79 | ND | Negative | Negative |
| C031000279 | yes | yes | yes | *Aspergillus fumigatus* (BAL) | Proven | 27 | 31 | ND | 1 Positive (28) | Can (-1) Asp (28) |
| C031000280 | yes | yes | yes | *Aspergillus flavus* (Wound) | Proven | 56 | 58 | ND | 3 Positive (43; 57; 63) | Asp (43) |
| C035000205 | yes | yes | yes | Mold (Pleural fluid) | Proven | 28 | 28 | ND | Negative | Can (31; 33) |
| C035000220 | yes | no | no | *Aspergillus flavus* (Pleural fluid) | Proven | 26 | 84 | FLZ = 64; POS = 0.06 | 1 Positive (78) | Asp ( 35; 78) |
| C046000260 | yes | yes | no | *Candida krusei* (Blood) | Proven | 36 | 36 | FLZ = 32; POS = 0.125 | Negative | Negative |
| C051000538 | yes | yes | yes | *Aspergillus species* (bronchial washings) | Proven | 14 | 17 | ND | 1 Positive (17) | Asp (-2) |
| I005000521 | yes | yes | yes | *Candida glabrata* (esophageal biopsy) | Proven | 28 | 31 | ND | Negative | Asp (31) |
| I012000076 | yes | yes | no | *Candida parapsilosis* (Blood) | Proven | 7 | 30 | ND | Negative | Can (-3; 10) Asp (47) |
| I044000600 | yes | yes | no | *Candida albicans* (esophageal lesions) | Proven | 2 | 2 | ND | Negative | Negative |
| I045000440 | yes | yes | yes | *Rhizomucor miehei* (Nasal biopsy) | Proven | 60 | 61 | ND | Negative | Asp (43) |
| C004000195 | yes | yes | yes | *Aspergillus species* | Probable | 14 | 18 | ND | Negative | Negative |
| C012000014 | yes | yes | yes | *Aspergillus fumigatus*(sputum and BAL) | Probable | 37 | 37 | ND | Negative | Asp (13) |
| C019000340 | yes | yes | yes | *Aspergillus species* | Probable[#] | 32 | 79 | ND | 3 Positive (72; 79; 82) | Negative |
| C025000034 | yes | yes | yes | *Aspergillus species* | Probable[#] | 57 | 28 | ND | 2 Positive (26, 28) | Negative |
| C046000259 | yes | yes | yes | *Aspergillus species* | Probable[#] | 39 | 38 | ND | 2 Positive (39) | Asp (39) |
| I002000868 | yes | no | no | *Aspergillus species* (sputum) | Probable | 113 | 35 | FLZ = 256; POS = 0.03 | 2 Positive (15; 57) | Negative |
| I005000535 | yes | yes | yes | *Aspergillus species* | Probable[#] | 14 | 23 | ND | 2 Positive (14; 27) | Can (-1) Asp (14; 21) |
| I011000740 | yes | yes | yes | *Aspergillus species* (sputum) | Probable | 11 | 14 | ND | 1 Positive (15) | Asp (15) |
| I012000071 | yes | yes | yes | *Aspergillus species* | Probable[#] | 45 | 80 | ND | 1 Positive (80)[&] | Negative |

[@] the prefix number indicated number of serum samples tested; [$] minimum inhibitory concentration (MIC) reading after 48 hours of incubation; ND = not done; [&] = case report indicate multiple positive tests but results not given; Can = positive with *Candida* probe; Asp = positive with *Aspergillus* probe; [#] based on antigen assay; FLZ = fluconazole; POS = posaconazole; IFI = invasive fungal infections; ** source of culture

Table 6: Continued

| SubID | Treated | MITT | Evaluable | Pathogen (source**) | IFI | Treatment duration | Day of onset of IFI after first dose | MIC (µg/ml)[$] | Aspergillus antigen result (day of result)[@] | PCR result (day of result) |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Fluconazole*** | | | | | | | | | | |
| I019000033 | yes | yes | yes | *Aspergillus fumigatus* (BAL) | Probable | 58 | 57 | ND | 2 Positive (43; 57) | Negative |
| I028000785 | yes | no | no | *Aspergillus species* (sputum) | Probable | 23 | 24 | ND | Negative | Negative |
| I035000495 | yes | yes | no | *Aspergillus species* (BAL) | Probable | 6 | 57 | ND | 3 Pos ( 1; 16; 29) | Negative |
| I043000783 | yes | yes | yes | *Aspergillus terreus* (lung biopsy) | Probable | 80 | 45 | ND | 10 Positive (27 to 98)* | Asp (43) |
| I046000200 | yes | yes | yes | *Aspergillus fumigatus* (BAL) | Probable | 16 | 18 | ND | 2 Positive (19)* | Can (14) |
| ***Posaconazole*** | | | | | | | | | | |
| C009000342 | yes | yes | yes | *Candida krusei* (urine) | Proven | 7 | 48 | ND | 1 Positive (42) | Asp (42) |
| C015000137 | yes | yes | yes | *Pseudoallescheria boydii* (multiple sites) | Proven | 29 | 31 | ND | Negative | Negative |
| C015000672 | yes | yes | no | *Aspergillus fumigatus* + *Candida glabrata* (Bronchial washing) | Proven | 2 | 18 | ND | 1 Positive (16) | Asp ( -1:16) |
| C020000120 | yes | yes | no | Mold (lung biopsy) | Proven | 4 | 9 | ND | Negative | Asp (-2) |
| C025000022 | yes | yes | yes | *Candida glabrata* (Blood) | Proven | 33 | 75 | ND | 2 Positive (59;70) | Negative |
| C025000030 | yes | yes | yes | *Candida glabrata* (Blood) | Proven | 17 | 14 | FLZ = NA; POS = 8 | Negative | ND |
| C035000217 | no | no | no | *Candida species* (Blood) | Proven | . | 20 | ND | Negative | Can (7) Asp (7) |
| C043000516 | yes | yes | no | Mold (lung biopsy) | Proven | 4 | 104 | | Negative | Negative |
| I060000948 | yes | no | no | *Aspergillus fumigatus* (Bronchial washing) | Proven | 42 | 62 | FLZ = 64; POS = NA | Negative | Negative |
| I066000618 | yes | yes | yes | *Trichosporon biegelii* (Blood) | Proven | 25 | 22 | FLZ = 1.0; POS = 0.06 | 1 Positive (15) | Negative |
| I071000953 | yes | yes | yes | *Scedosporium prolificans* (BAL) | Proven | 14 | 80 | ND | Negative | Asp (-1; 13) |
| C009000341 | yes | yes | yes | *Aspergillus species* | Probable[#] | 112 | 105 | ND | 3 positive (76, 105, 112) | Negative |
| C030000079 | yes | yes | yes | *Aspergillus species* | Probable[#] | 45 | 26 | ND | 1 Positive (14) | Asp (14) |
| I004000048 | yes | yes | yes | *Aspergillus species* | Probable[#] | 13 | 48 | ND | 5 Positive (35,38,43,45,49) | Asp (63; 72; 79) |
| I021000301 | yes | no | no | *Aspergillus species* (histology lung biopsy) | Probable | 66 | 78 | ND | Negative | Asp (78) |
| **I054000475** | **yes** | **yes** | **yes** | ***Aspergillus species*** | **Probable[#]** | **86** | **87** | **ND** | **1 Positive (NS)*** | **Asp (100; 136)** |

# probable based on antigen test results; ** source of culture;

* 1 of positive result was using BAL sample;

[@] the prefix number indicated number of serum samples tested; $ minimum inhibitory concentration (MIC) reading after 48 hours of incubation; ND = not done;

Can = positive with *Candida* probe; Asp = positive with *Aspergillus* probe; [#] based on antigen assay; FLZ = fluconazole; POS = posaconazole; IFI = invasive fungal infections;

Table 7: Pathogen group associated with proven and probable^ IFIs during the primary time period (16 weeks) in the all treated and evaluable population.

| Pathogen group | Fluconazole | | Posaconazole | |
|---|---|---|---|---|
| | Treated | Evaluable | Treated | Evaluable |
| *Aspergillus fumigatus* | 5 | 5 | 2 | 0 |
| *Aspergillus flavus* | 3 | 2 | 0 | 0 |
| *Aspergillus terreus* | 1 | 1 | 0 | 0 |
| *Aspergillus niger* | 1 | 1 | 0 | 0 |
| *Aspergillus species* | 11 | 8 | 5 | 4 |
| *Candida albicans* | 1 | 0 | 0 | 0 |
| *Candida glabrata* | 1 | 1 | 2 | 2 |
| *Candida krusei* | 1 | 0 | 1 | 1 |
| *Candida parapsilosis* | 1 | 0 | 0 | 0 |
| *Rhizomucor miehei* | 1 | 1 | 0 | 0 |
| *Pseudoallescheria boydii* | 0 | 0 | 1 | 1 |
| *Scedosporium prolificans* | 0 | 0 | 1 | 1 |
| *Trichosporon biegelii* | 0 | 0 | 1 | 1 |
| Other mold | 1 | 1 | 2 | 0 |
| Total | 27 | 20 | 15 | 10 |

^For probable IFIs, the species were isolated from sputum, BAL or biopsy samples.

Ten evaluable patients in the FLZ arm and 2 evaluable patients in the POS arm developed proven or probable invasive fungal infections during the post-therapy period i.e. after 16 weeks (Table 8). In the FLZ arm, the infections were due to *A. fumigatus* (n = 4), *Aspergillus* species (n = 4), *Candida* species (n = 1), and an unidentified mold in one patient. In the POS arm, the infections were due to *Aspergillus* species (n = 2). Overall, the activity of POS appears to be similar to FLZ for proven IFIs.

Table 8: Invasive fungal infections (IFIs) detected during post-treatment period in all treated patients. For probable IFIs, the species were isolated from sputum, BAL or biopsy samples.

| SubID | MITT | Evaluable | Treatment | Pathogen | IFI | Treatment duration (days) | Day of onset of IFI after first dose |
|---|---|---|---|---|---|---|---|
| C012000002 | no | no | Fluconazole | *Candida glabrata* | proven | 116 | 143 |
| C012000009 | yes | no | Fluconazole | *Aspergillus fumigatus* | proven | 47 | 120 |
| C035000211 | yes | yes | Fluconazole | *Aspergillus species* | proven | 125 | 129 |
| C042000497 | no | no | Fluconazole | *Candida glabrata* | proven | 114 | 172 |
| C043000520 | no | no | Fluconazole | *Candida glabrata* | proven | 113 | 168 |
| I015000807 | yes | yes | Fluconazole | *Aspergillus fumigatus* | proven | 114 | 113 |
| I043000766 | yes | yes | Fluconazole | *Candida species* | proven | 112 | 135 |
| C003000458 | yes | no | Fluconazole | *Aspergillus species* | probable | 1 | 144 |
| C012000662 | yes | yes | Fluconazole | *Aspergillus fumigatus* | probable | 107 | 179 |
| C043000517 | yes | yes | Fluconazole | *Aspergillus species* | probable | 110 | 132 |
| C046000241 | yes | yes | Fluconazole | *Mold* | probable | 112 | 221 |
| I020000009 | yes | yes | Fluconazole | *Aspergillus species* | probable | 113 | 145 |
| I054000474 | yes | yes | Fluconazole | *Aspergillus species* | probable | 39 | 117 |
| I066000617 | yes | yes | Fluconazole | *Aspergillus fumigatus* | probable | 112 | 161 |
| I071000367 | yes | yes | Fluconazole | *Aspergillus fumigatus* | probable | 76 | 118 |
| C017000639 | no | no | Posaconazole | *Candida species* | proven | 122 | 132 |
| C035000207 | no | no | Posaconazole | *Candida glabrata* | proven | 138 | 165 |
| C012000664 | yes | yes | Posaconazole | *Aspergillus species* | probable | 72 | 119 |
| C050000419 | yes | yes | Posaconazole | *Aspergillus species* | probable | 114 | 173 |

Oral swish cultures were collected during the study to evaluate fungal colonization. In subjects who received >14 days of antifungal therapy, the MICs of oral isolates of the same species obtained at baseline (defined as an isolate cultured before start of treatment or within 7 days of treatment start) and at end of treatment (EOT; defined as an isolate cultured less than 30 days before EOT or within 7 days post-EOT) were compared. The number of subjects for whom both pre- and post-treatment pathogen data were available for the FLZ and POS treatment arms were 24 and 21, respectively. In both groups, the principal pathogens were *C. albicans* and *C. glabrata* (Table 9). *C. krusei* was only detected in 4 subjects treated with FLZ. A ≥ 4 fold increase in POS MIC alone was observed in 4 *C. glabrata* isolates and 2 *C. albicans* isolates from POS treated patients compared to increases in FLZ MIC in 3 *C. glabrata* isolates and 4 *C. albicans* isolates from FLZ treated patients (Tables 9 and 10). Cross-resistance between POS and other azoles were observed in isolates from 4 subjects treated with FLZ and one subject treated with POS. The isolates exhibited a >4 fold decrease in susceptibility to all three azoles tested (POS, FLZ and ITZ) at EOT. Of the five EOT isolates, four were *C. glabrata* and one was *C. albicans*. The study suggests a potential for development of drug resistance in patients receiving POS prophylaxis and cross-resistance between azole drugs.

Table 9: Listing of susceptibilities for isolates that were the same at baseline and end of treatment (FLU = FLZ).

| Site/Subject | Study Treatment | Pathogen | Source | POS BL MIC | POS EOT MIC | FLU BL MIC | FLU EOT MIC | ITR BL MIC | ITR EOT MIC | AMB BL MIC | AMB EOT MIC |
|---|---|---|---|---|---|---|---|---|---|---|---|
| C4/163 | FLU | Candida albicans | Mouth | 0.0075 | 0.0075 | 4 | 8 | 0.0075 | 0.03 | 0.25 | 0.5 |
| C4/187 | FLU | Candida albicans | Mouth | 0.0075 | 0.0075 | 0.25 | 0.0625 | 0.0075 | 0.0075 | 0.125 | 0.125 |
| C7/462 | FLU | Candida albicans | Mouth | **0.0075** | **0.06** | 8 | 8 | 0.06 | 0.03 | 0.25 | 0.25 |
| C25/031 | FLU | Candida albicans | Mouth | 0.0075 | 0.0075 | **16** | **128** | 0.03 | 0.06 | 0.25 | 0.125 |
| I4/042 | FLU | Candida albicans | Mouth | 0.0075 | 0.0075 | **0.0625** | 1 | **0.0075** | **0.06** | 0.25 | 0.25 |
| I4/056 | FLU | Candida albicans | Mouth | 0.0075 | 0.0075 | 0.0625 | 0.0625 | 0.0075 | 0.0075 | 0.25 | 0.25 |
| I41/525 | FLU | Candida albicans | Mouth | **0.0075** | **16** | **0.0625** | **128** | **0.0075** | **16** | 0.125 | 0.5 |
| I43/663 | FLU | Candida albicans | Mouth | 0.0075 | 0.0075 | 0.0625 | 0.0625 | 0.0075 | 0.0075 | 0.25 | 0.125 |
| I55/601 | FLU | Candida albicans | Mouth | 0.0075 | 0.0075 | 0.0625 | 0.0625 | 0.0075 | 0.0075 | 0.125 | 0.125 |
| I71/352 | FLU | Candida albicans | Mouth | 0.0075 | 0.03 | 0.5 | 2 | 0.0075 | 0.03 | 0.25 | 0.25 |
| I71/655 | FLU | Candida albicans | Mouth | 0.03 | 0.03 | 8 | 4 | 0.06 | 0.125 | 0.25 | 0.25 |
| C10/002 | FLU | Candida glabrata | Mouth | **0.5** | **4** | **16** | **64** | **1** | **16** | 1 | 0.5 |
| C15/135 | FLU | Candida glabrata | Mouth | 0.125 | 0.5 | 8 | 8 | 0.25 | 1 | 0.25 | 0.25 |
| C16/063 | FLU | Candida glabrata | Mouth | 0.125 | 0.5 | 8 | 8 | 0.5 | 0.5 | 0.25 | 0.5 |
| C42/497 | FLU | Candida glabrata | Mouth | 0.5 | 2 | 16 | 32 | 1 | 8 | 0.25 | 0.5 |
| I15/607 | FLU | Candida glabrata | Mouth | 0.25 | 16 | 16 | **128** | **0.5** | **16** | 0.5 | 0.5 |
| I20/370 | FLU | Candida glabrata | Mouth | 16 | 4 | 128 | 128 | 4 | 16 | 0.25 | 0.25 |
| I35/491 | FLU | Candida glabrata | Mouth | **0.25** | **2** | **4** | **32** | **0.25** | **2** | 0.25 | 0.25 |
| I19/033 | FLU | Candida krusei | Mouth | 0.25 | 0.25 | 32 | 32 | 0.25 | 0.25 | 1 | 0.5 |
| I43/245 | FLU | Candida krusei | Mouth | 0.125 | 0.25 | 32 | 64 | 0.25 | 0.5 | 0.5 | 0.25 |
| I43/763 | FLU | Candida krusei | Mouth | 0.125 | 0.5 | 64 | 128 | 0.25 | 0.25 | 0.25 | 0.5 |
| I54/478 | FLU | Candida krusei | Mouth | 0.25 | 0.125 | 64 | 64 | 0.5 | 1 | 0.25 | 0.25 |
| C25/037 | FLU | Saccharomyces cerevisiae | Mouth | 0.03 | 0.06 | 0.5 | 0.5 | 0.03 | 0.06 | 0.25 | 0.25 |
| I41/525 | FLU | Saccharomyces cerevisiae | Mouth | 0.5 | 0.5 | 4 | 4 | 0.5 | 0.5 | 0.06 | 0.06 |
| C4/192 | POS | Candida albicans | Mouth | 0.03 | 0.03 | 0.5 | 1 | 0.06 | 0.06 | 0.125 | 0.125 |
| C31/262 | POS | Candida albicans | Mouth | 0.0075 | 0.0075 | **0.25** | 2 | **0.0075** | **0.06** | 0.125 | 0.25 |
| I16/340 | POS | Candida albicans | Mouth | 0.0075 | 0.03 | 0.0625 | 0.25 | 0.0075 | 0.0075 | 0.25 | 0.25 |
| I21/301 | POS | Candida albicans | Mouth | 0.0075 | 0.03 | 0.0625 | 0.25 | **0.0075** | **0.25** | 0.125 | 0.25 |
| I28/136 | POS | Candida albicans | Mouth | 0.0075 | 0.0075 | 0.25 | 0.0625 | 0.0075 | 0.0075 | 0.125 | 0.25 |
| I28/137 | POS | Candida albicans | Mouth | 0.03 | 0.03 | 2 | 4 | 0.06 | 0.25 | 0.25 | 0.25 |
| I48/664 | POS | Candida albicans | Mouth | 0.03 | 0.0075 | 0.0625 | 0.0625 | 0.0075 | 0.0075 | 0.125 | 0.125 |
| I59/641 | POS | Candida albicans | Mouth | 0.06 | 0.06 | 8 | 16 | 0.25 | 0.25 | 0.125 | 0.125 |
| I51/637 | POS | Candida albicans | Mouth | 0.03 | 0.0075 | 0.25 | 0.0625 | 0.06 | 0.0075 | 0.25 | 0.25 |
| C4/185 | POS | Candida glabrata | Mouth | **0.25** | **2** | 8 | 32 | 0.5 | 2 | 0.5 | 0.5 |
| C7/474 | POS | Candida glabrata | Mouth | **0.25** | **4** | 16 | 64 | 4 | 8 | 0.25 | 0.25 |
| C16/031 | POS | Candida glabrata | Mouth | 1 | 1 | 16 | 64 | 1 | 0.25 | 0.5 | 0.25 |
| C25/030 | POS | Candida glabrata | Mouth | 16 | 8 | 128 | 128 | 16 | 16 | 0.5 | 0.5 |
| I32/280 | POS | Candida glabrata | Mouth | 0.25 | 0.25 | 16 | 4 | 0.25 | 0.125 | 1 | 0.5 |
| I43/246 | POS | Candida glabrata | Mouth | 1 | 1 | 16 | 8 | 2 | 2 | 0.25 | 0.25 |
| I43/575 | POS | Candida glabrata | Mouth | **0.25** | **4** | 4 | **128** | **0.25** | **8** | 0.25 | 0.25 |
| I43/876 | POS | Candida glabrata | Mouth | 1 | 1 | 16 | 32 | 1 | 1 | 0.25 | 0.25 |
| I65/270 | POS | Candida glabrata | Mouth | **0.06** | 1 | 8 | 8 | **0.125** | 1 | 1 | 2 |
| I51/622 | POS | Candida inconspicua | Mouth | 0.125 | 0.125 | 32 | 32 | 0.25 | 0.25 | 0.125 | 0.125 |
| C43/512 | POS | Saccharomyces cerevisiae | Mouth | 1 | 4 | 8 | 32 | 0.5 | **4** | 0.06 | 0.125 |
| I54/661 | POS | Saccharomyces cerevisiae | Mouth | 0.5 | 0.5 | 8 | 4 | 0.5 | 0.5 | 0.06 | 0.015 |

AMB = amphotericin B; BL = baseline; EOT = end of treatment; FLU = fluconazole; ITR = itraconazole; MIC = minimum inhibitory concentration; POS = posaconazole.

Note: >4-fold increases in MIC are in bold text.

Table 10: Increase in MIC for *Candida* isolates in the posaconazole and fluconazole arms.

| Fold increase in MIC | POS (n = 21) | FLZ (n = 24) |
|---|---|---|
| *C. albicans* | | |
| ≥ 4 | 2 | 4 |
| > 4 | - | 3 |
| *C. glabrata* | | |
| ≥ 4 | 4 | 3 |
| >4 | 4 | 2 |

**4.2. Study P01899**

This was a Phase 3, randomized, evaluator-blinded, active control, parallel group, multi-center study. It was designed to assess the safety, tolerance, and efficacy of POS as a prophylactic agent against IFI in high-risk subjects with prolonged neutropenia. Subjects from United Sates, Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, Dominican Republic, Ecuador, El Salvador, France, Germany, Greece, Guatemala, Italy, Mexico, Netherlands, Panama, Peru, Poland, Portugal, Puerto Rico, Singapore, South Africa, Spain, Sweden, and United Kingdom were enrolled. Protocol-eligible subjects were randomized (1:1) to receive either 600 mg of POS (200 mg TID) or standard azole therapy (FLZ [400 mg QD] or ITZ [200 mg BID]). Treatment was continued until recovery from neutropenia or occurrence of an IFI for a maximal period of 12 weeks (84 calendar days) from randomization. Follow-up visits for all subjects (including those who discontinued treatment early for any reason) were to occur 30 days after the last dose of study drug or 100 days after randomization. All subjects had baseline and periodic evaluations for the presence of fungal infection as described in the previous study. As in the previous study, Dr. Rinaldi's Laboratory served as the central laboratory for fungal speciation and *in vitro* susceptibility testing while Dr. Holger's Laboratory performed the PCR testing. The *Aspergillus* galactomannan antigen testing was done by [redacted] (Belgium) using the FDA approved [redacted] Aspergillus antigen kit. A treatment failure was defined as the presence of a proven or probable IFI, ≥ 4 days of empiric parenteral (IV) antifungal treatment for a suspected IFI, >3 consecutive days or ≥ 10 cumulative days of IV alternative study medication during the treatment phase, or discontinuation due to an adverse event considered possibly or probably related to study drug. Subjects who withdrew from the study for any reason and were subsequently lost to follow-up during the treatment phase were also considered as treatment failures.

The number of subjects with proven, probable, and possible invasive fungal infections in the different populations during the oral treatment phase is shown in Table 11. The oral treatment duration varied from 1 to 151 days (mean treatment duration = 25 for POS; 21 for FLZ). The following discussion focuses on the primary endpoint of proven and probable infections during treatment. Proven breakthrough fungal infections were seen in 5 patients treated with FLZ and 4 patients treated with POS. No proven breakthrough fungal infections were observed in the ITZ arm. The number of probable breakthrough infections were higher in the FLZ treated patients (n = 14) compared to ITZ (n = 6) or POS (n = 3).

In the evaluable populations, 18 FLZ treated patients developed proven or probable invasive fungal infections during treatment (Table 11). In 10 patients, the diagnosis of probable infection was based on *Aspergillus* antigen or serology test results (the serology test was not specified and antibody titers were not shown) using serum samples. For 3 patients, the diagnosis was based on a single positive *Aspergillus* antigen test using serum samples. Repeat testing of the positive serum sample and testing of additional serum samples is recommended by the manufacturer of the kit. As discussed in the previous study, the results of the aspergillus antigen test should be interpreted with caution and in conjunction with other clinical and radiological findings. The PCR test was performed for exploratory reasons and not used in diagnosis of IFI. The results of the PCR test did not correlate with occurrence of invasive fungal infections or presence of galactomannan antigen (Table 12). As shown in Tables 12 and 13, the majority of proven or probable invasive fungal infections were due to *Aspergillus* species, *A. fumigatus* or *A. flavus* (n = 14), and the remaining infections were due to *Candida* species other than *C. albicans* (n = 2),

*Rhizopus arrhizus* (n = 1) or *Pseudoallescheria boydii* (n = 1). Invasive infections due to these pathogens were identified within 5 to 81 days of initiating FLZ prophylaxis.

Table 11: The number of patients who developed proven, probable, or possible invasive fungal infections during treatment in the different populations.

| ***All randomized*** | | | |
|---|---|---|---|
| **IFIs** | **Fluconazole (n = 240)** | **Posaconazole (n = 304)** | **Itraconazole (n = 58)** |
| Proven | 5 | 4 | 0 |
| Probable | 14 | 3 | 6 |
| Possible | 46 | 59 | 8 |
| ***All treated and MITT*** | | | |
| **IFIs** | **Fluconazole (n = 238)** | **Posaconazole (n = 297)** | **Itraconazole (n = 54)** |
| Proven | 5 | 4 | 0 |
| Probable | 14 | 3 | 6 |
| Possible | 45 | 59 | 8 |
| ***Evaluable*** | | | |
| **IFIs** | **Fluconazole (n = 212)** | **Posaconazole (n = 265)** | **Itraconazole (n = 51)** |
| Proven | 5 | 4 | 0 |
| Probable | 13 | 3 | 6 |
| Possible | 41 | 55 | 8 |

IFIs = invasive fungal infections

Seven POS treated patients developed proven or probable invasive fungal infections during treatment. The invasive infections were identified on either the first day of treatment or 53 days after initiation of POS prophylaxis (Table 12). The *Aspergillus* antigen test results were used for diagnosis of probable infections in 2 out of 3 patients. In one patient, the result was based on testing of a single serum sample. As shown in Tables 12 and 13, the invasive fungal infections were due to *Aspergillus* species (n = 2), *C. glabrata* (n = 2), or mixed infections due to *Candida* species and mold (n = 2). One patient had infection due to *Pneumocystis carinii.*

None of the patients receiving ITZ prophylaxis developed a proven fungal infection during treatment. Six patients were identified as having probable fungal infections (Tables 11 and 12). The *Aspergillus* antigen test results were used for diagnosis of 4 out of 6 probable infections. In one patients, the results was based on one positive serum sample. Of the 6 patients, 4 had infections due to *Aspergillus* species, 1 due to *A. fumigatus* and 1 due to *Pneumocystis carinii* (Table 13).

During the post-treatment phase, 2 FLZ treated patients developed proven or probable IFI due to *A. flavus* or *Aspergillus* species. In the POS arm, 2 patients developed proven or probable IFIs due to *Kluyveromyces maxianus* or *Aspergillus* species. In the ITZ arm, 1 patient developed a proven infection due to *Aspergillus* species. Thus, there was no difference in the incidence of proven and probable IFIs between the treatment groups in the post-treatment phase.

The *in vitro* susceptibility testing was performed for 6 breakthrough isolates (4 *Aspergillus* isolates and 2 *Candida* isolates). The POS MICs for all 6 isolates were $\leq 0.125$ µg/ml.

Overall, the activity of POS appears to be similar to FLZ for proven breakthrough infections. However, probable breakthrough infections in the POS arm were lower than that in the FLZ and ITZ arms.

Table 12: Pathogen identified as cause of invasive fungal infection during treatment with posaconazole, fluconazole or itraconazole

| SubID | Treated | MITT | Evaluable | Pathogen (culture source) | IFI | Treatment duration | Day of onset of IFI after first dose | MIC at 48 hours (µg/ml) | Aspergillus antigen result (day) | PCR result (day) |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Fluconazole*** | | | | | | | | | | |
| 0003001284 | yes | yes | yes | *Aspergillus species* (small intestine) | Proven | 52 | 52 | ND | 5 Positive (45-52) | Negative |
| 0050001155 | yes | yes | yes | *Rhizopus arrhizus* (Nasal tissue) | Proven | 6 | 4 | ND | Negative | Asp (1) |
| 0057001498 | yes | yes | yes | *Pseudallescheria boydii* (wound sample) | Proven | 12 | 15 | ND | Negative | Negative |
| 0074001493 | yes | yes | yes | *Candida glabrata* (blood) | Proven | 27 | 28 | ND | Negative | Negative |
| 0148001248 | yes | yes | yes | *Candida krusei* + *Candida parapsilosis* (blood) | Proven | 12 | 10 | ND | Negative | ND |
| 0002001045 | yes | yes | yes | *Aspergillus fumigatus* (BAL) | Probable | 37 | 33 | FLZ = >64<br>Posa = 0.125 | Negative | Asp (2, 15) |
| 0002001103 | yes | yes | yes | *Aspergillus species* (NS)** | Probable | 12 | 6 | ND | 4 Positive ( 8-14) | Negative |
| 0002001211 | yes | yes | yes | *Aspergillus species* | Probable^ | 5 | 5 | ND | 4 Positive ( 1-14) | Negative |
| 0002001307 | yes | yes | yes | *Aspergillus species* | Probable# | 10 | 14 | ND | 6 Positive (14-138) | Asp (2) |
| 0003001563 | yes | yes | no | *Aspergillus species* | Probable# | 3 | 7 | ND | 6 Positive (10-30) | Negative |
| 0008001352 | yes | yes | yes | *Aspergillus species* | Probable# | 12 | 7 | ND | 1 Positive (7) | Negative |
| 0041001215 | yes | yes | yes | *Aspergillus species* | Probable# | 16 | 10 | ND | 2 Positive (13, 19) | ND |
| 0041001242 | yes | yes | yes | *Aspergillus flavus* (BAL) | Probable | 18 | 11 | FLZ = 64<br>Pos = 0.06 | 4 Positive (12-19) | ND |
| 0041001461 | yes | yes | yes | *Aspergillus species* | Probable# | 20 | 14 | ND | 2 Positive (10, 14) | Asp (1,7) |
| 0041001510 | yes | yes | yes | *Aspergillus species* | Probable# | 10 | 10 | ND | 1 Positive (11) | Negative |
| 0068001560 | yes | yes | yes | *Aspergillus species* | Probable# | 12 | 12 | ND | 3 Positive (13-16) | Negative |
| 0079001380 | yes | yes | yes | *Aspergillus species* | Probable# | 82 | 81 | ND | 2 Positive (82, 112) | Asp (65) |
| 0102001342 | yes | yes | yes | *Aspergillus flavus* (BAL) | Probable | 20 | 8 | ND | 6 Positive (10-52) | Negative |
| 0139001081 | yes | yes | yes | *Aspergillus species* | Probable# | 12 | 12 | ND | 1 Positive (14) | Asp (3, 16) |

# probable based on antigen test results

@ the prefix number indicated number of serum samples tested; $ minimum inhibitory concentration (MIC) reading after 48 hours of incubation; ND = not done; Can = positive with *Candida* probe; Asp = positive with *Aspergillus* probe; # based on antigen assay; FLZ = fluconazole; POS = posaconazole; IFI = invasive fungal infections; NS = not specified; ^probable infection based by serology

** diagnosis at autopsy

Shaded rows show patients with probable infection based on results from a single aspergillus antigen test.

Table 12: Continued

| SubID | Treated | MITT | Evaluable | Pathogen (culture source) | IFI | Treatment duration | Day of onset of IFI after first dose | MIC (μg/ml) | Aspergillus antigen result (day) | PCR result (day) |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Posaconazole*** | | | | | | | | | | |
| 0002001271 | yes | yes | yes | *Pneumocystis carinii* (NS)** | Proven | 45 | 50 | ND | Negative | Negative |
| 0015001415 | yes | yes | yes | *Candida glabrata* (blood) | Proven | 48 | 43 | FLZ = 4<br>Pos = 0.125 | Negative | Asp (42) |
| 0041001329 | yes | yes | yes | *Candida tropicalis + mold* (blood and BAL) | Proven | 5 | 0 | ND | Negative | Negative |
| 0057001492 | yes | yes | yes | *Candida glabrata* (blood) | Proven | 12 | 7 | FLZ = 8<br>Pos = 0.5 | Negative | Can (7) |
| 0010001371 | yes | yes | yes | *Mold + Candida species* (BAL) | Probable | 9 | 10 | FLZ = 4<br>Pos = 0.125 | ND | ND |
| 0015001239 | yes | yes | yes | *Aspergillus species* | Probable[#] | 54 | 53 | ND | 11 Positive (12, 92-99) | ND |
| 0054001468 | yes | yes | yes | *Aspergillus species* | Probable[#] | 92 | 43 | ND | 1 Positive (43) | Asp (51, 71, 78) |
| ***Itraconazole*** | | | | | | | | | | |
| 0010001425 | yes | yes | yes | *Aspergillus species* | Probable[#] | 9 | 8 | ND | 2 Positive (3; 11) | Negative |
| 0015001279 | yes | yes | yes | *Aspergillus species* | Probable[#] | 17 | 16 | ND | 2 Positive (17) | Asp (10) |
| 0015001517 | yes | yes | yes | *Aspergillus species* | Probable[#] | 7 | 6 | ND | 16 Positive (8 to 22) | Negative |
| 0084001179 | yes | yes | yes | *Pneumocystis carinii* (BAL) | Probable | 16 | 16 | ND | Negative | Can (1), Asp (100) |
| 0096001146 | yes | yes | yes | *Aspergillus fumigatus* (NS) | Probable | 19 | 18 | FLZ = 64<br>Pos = 0.125 | Negative | Asp (1) |
| 0125001109 | yes | yes | yes | *Aspergillus species* | Probable[#] | 96 | 20 | ND | 1 Positive (21) | Asp (27, 39, 46) |

# probable based on antigen test results

[@] the prefix number indicated number of serum samples tested; [$]minimum inhibitory concentration (MIC) reading after 48 hours of incubation; ND = not done; Can = positive with *Candida* probe; Asp = positive with *Aspergillus* probe; [#] based on antigen assay; FLZ = fluconazole; POS = posaconazole; IFI = invasive fungal infections; NS = not specified; ^probable infection based by serology

** diagnosis at autopsy

Shaded rows show patients with probable infection based on results from a single aspergillus antigen test.

Table 13: Pathogen group associated with proven and probable^ IFIs during treatment in the treated and evaluable population.

| Pathogen group | Fluconazole | | Posaconazole | | Itraconazole | |
|---|---|---|---|---|---|---|
| | Treated | Evaluable | Treated | Evaluable | Treated | Evaluable |
| *Aspergillus fumigatus* | 1 | 1 | 0 | 0 | 1 | 1 |
| *Aspergillus flavus* | 2 | 2 | 0 | 0 | 0 | 0 |
| *Aspergillus species* | 12 | 11 | 2 | 2 | 4 | 4 |
| *Candida glabrata* | 1 | 1 | 2 | 2 | 0 | 0 |
| *Candida krusei+ Candida parapsilosis* | 1 | 1 | 0 | 0 | 0 | 0 |
| *Candida tropicalis + Mold* | 0 | 0 | 1 | 1 | 0 | 0 |
| *Candida species + Mold* | 0 | 0 | 1 | 1 | 0 | 0 |
| *Rhizomucor arrhizus* | 1 | 1 | 0 | 0 | 0 | 0 |
| *Pseudoallescheria boydii* | 1 | 1 | 0 | 0 | 0 | 0 |
| *Pneumocystis carinii* | 0 | 0 | 1 | 1 | 1 | 1 |
| Total | 19 | 18 | 7 | 7 | 6 | 6 |

^For probable IFIs, the species were isolated from BAL samples.

### 4.3. Interpretive criteria:

No interpretive criteria for *in vitro* susceptibility testing of fungi to POS have been proposed by the sponsor nor does the information provided by the sponsor support establishment of interpretive criteria.

## 5. CONCLUSIONS

The sponsor is seeking approval of POS for the prophylaxis of IFIs in high-risk patients (≥ 13 years of age) with prolonged neutropenia or who have undergone hematopoietic stem cell transplantation. The proposed dose is 600 mg/day POS orally (as divided doses with meals) until recovery from neutropenia or immunosuppression.

POS exhibits antifungal activity by inhibition of lanosterol 14α-demethylase, an enzyme involved in ergosterol biosynthesis. This results in accumulation of methylated sterols. These studies were done using *Candida* species, *Aspergillus* species and Zygomycetes. The *in vitro* activity of POS against yeasts and mold was similar to that observed in studies reviewed previously

There are several mechanisms by which fungi develop resistance to azoles. These include target enzyme alterations, expression of efflux proteins, and development of compensatory pathways. Two *Candida* isolates with reduced susceptibility to azoles including posaconazole were shown to have mutations in the *ERG3* gene. The inactivation of sterol $\Delta^{5,6}$-desaturase enzyme encoded by *ERG3* gene prevents accumulation of methylated sterols and cause azole resistance.

Two studies (C/I98-316 and P01899) were included in this submission to support the prophylaxis indication. The IFI status in these studies was characterized using the EORTC - MSG standardized definitions. For proven infections, the microbiology criteria included positive culture from blood or a sterile site or histopathological evidence of hyphae from needle

aspirations or biopsy samples. For probable infections, the microbiological criteria included positive culture from sites that may be colonized (for example, sputum, BAL fluid, sinus aspirate) or positive result for *Aspergillus* antigen in specimens of BAL, CSF, or ≥ 2 serum samples. The *Aspergillus* antigen testing was performed using the [redacted] *Aspergillus* antigen kit which is approved in the US for use with serum samples and in conjunction with other procedures such as microbiological culture or histological and radiological assessments. The cut-off for a positive test (an OD index of ≥ 0.5) using the FDA approved kit is lower than that used in European countries previously (OD cut-off for positive test ≥ 1.5). The lower cut-off has been stated to improve sensitivity with minimum effect on specificity. However, a recent study showed that the accuracy of the test improved with a higher threshold. Additional microbiological assessments included *in vitro* susceptibility testing of breakthrough isolates and oral colonizers using CLSI recommended methods and PCR testing in a central laboratory. The PCR testing was only performed for exploratory purposes and was not used for diagnosis of fungal infection or fungal speciation.

In **study C/I98-316**, there were 20 FLZ treated patients and 10 POS treated patients who developed proven or probable invasive fungal infections during the primary time period (16 weeks). In 9 patients (FLZ, n = 5; POS, n = 4) with probable infection, the diagnosis was made using *Aspergillus* antigen test. In 3 of the 9 patients, the diagnosis was based on a single test result using serum or BAL samples. It should be noted that the *Aspergillus* antigen test approved for use with serum samples in the US is not truly diagnostic but provides information on probability of IFIs. Positive results should be interpreted with caution in conjunction with clinical and radiological findings as false-positive results due to presence of fungi other than *Aspergillus,* galactomannan from food, contamination from laboratory sources or administration of β-lactams are known to occur. In the FLZ arm, the invasive fungal infections were due to *Aspergillus* species (n = 17), *C. glabrata* (n = 1), *Rhizopus miehei* (n = 1) or unidentified mold. Invasive infections due to these pathogens were identified between 2 and 93 days after starting fluconazole prophylaxis. In the POS arm, the invasive fungal infections were due to *Aspergillus* species (n = 4), *C. glabrata* (n = 2), *C. krusei* (n = 1), *Pseudoallescheria boydii* (n = 1), *Scedosporium prolificans* (n = 1), and *Trichosporon biegelii* (n = 1). The invasive infections were identified between 9 and 105 days after starting POS prophylaxis. Limited *in vitro* susceptibility testing was performed on breakthrough isolates. The POS MICs against *Aspergillus* (n = 3) and *Candida* (n = 1) isolates were ≤ 0.125 μg/ml while POS MIC against 1 *Scedosporium* isolate was 8 μg/ml.

Oral swish cultures were performed to study fungal colonization in patients receiving prophylaxis. *Candida* isolates with reduced *in vitro* susceptibility to POS and/or other azoles were obtained after azole prophylaxis.

In **study P01899**, probable infections were diagnosed using the *Aspergillus* antigen test in 15 subjects (FLZ, n = 9; POS, n = 2; ITZ, n = 4). Few subjects had only one serum sample that was positive. As discussed previously, the results of the *Aspergillus* antigen test should be interpreted with caution in conjunction with clinical and radiological findings. There were 18 FLZ treated patients who developed proven or probable invasive fungal infections. The majority of invasive fungal infections were due to *Aspergillus* species, *A. fumigatus* or *A. flavus* (n = 14), and the

remaining infections were due to *Candida* species other than *C. albicans* (n = 2), *Rhizopus arrhizus* (n = 1) or *Pseudoallescheria boydii* (n = 1). Invasive infections due to these pathogens were identified between 5 to 81 days after starting FLZ prophylaxis. There were 7 POS treated patients who developed proven or probable invasive fungal infections. The invasive fungal infections were due to *Aspergillus* species (n = 2), *C. glabrata* (n = 2), or mixed infections due to *Candida* species and mold (n = 2). One patient had infection due to *Pneumocystis carinii*. The invasive infections were identified on either the first day of treatment or 53 days after starting POS prophylaxis. None of the patients receiving ITZ prophylaxis developed a proven fungal infection during the treatment period. Six patients were identified as having probable fungal infections. Of the 6 patients, 4 had infections due to *Aspergillus* species, one due to *A. fumigatus* and another due to *Pneumocystis carinii*.

The *in vitro* susceptibility testing was performed for 6 breakthrough isolates (4 *Aspergillus* isolates and 2 *Candida* isolates). The POS MICs for all 6 isolates were $\leq$ 0.125 µg/ml.

Although, a higher number of probable fungal infections were observed in FLZ and ITZ arms compared to POS arm, the numbers of proven breakthrough fungal infections were similar in the FLZ and POS arms. Overall, the activity of POS was similar to FLZ for proven IFIs in the two studies.

**6. LABEL**

2 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Microbiology-_____*

## 7. RECOMMENDATIONS

This NDA submission should be approved with respect to Microbiology.

Kalavati Suvarna
Microbiologist, HFD-590

**CONCURRENCES:**

Deputy Dir _____Signature _____Date
Micro TL _____Signature _____Date
CC:
Original IND
Division File
Review Micro
CSO/MillerK

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

/s/
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Kalavati Suvarna
6/20/2006 03:17:04 PM
MICROBIOLOGIST

Shukal Bala
6/20/2006 03:55:54 PM
MICROBIOLOGIST

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-003**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| **NDA: 22-003** | Submission Date(s): 12/22/2005 |
| **Drug** | Posaconazole |
| **Trade Name** | Noxafil |
| **Reviewer** | Seong H, Jang, Ph.D. (Primary and Pharmacometrics (PM))<br>Dakshina Chilukuri, Ph.D. (PM: Population PK) |
| **OCP Team Leader** | Philip M. Colangelo, Pharm.D., Ph.D. |
| **PM Team Leader** | Jogarao Gobburu, Ph. D. |
| **OCP Division** | DCP 4 |
| **OND division** | ODE IV DSPTP |
| **Sponsor** | Schering-Plough Corp. |
| **Relevant IND(s)** | 51,662 |
| **Submission Type; Code** | Original, 1S (NME) |
| **Formulation; Strength(s)** | Oral suspension 40 mg/mL (105 mL) |
| **Indication** | • Prophylaxis [redacted] in patients, 13 years of age and older, who are at high risk of developing these infections, such as hematopoietic stem cell transplant (HSCT) recipients or those with prolonged neutropenia<br>• Treatment of oropharyngeal candidiasis, including infections refractory to itraconazole and fluconazole |
| **Dosage and Administration** | Prophylaxis, [redacted]: 200 mg TID<br>Oropharyngeal Candidiasis:<br>Loading dose of 200 mg QD, then 100 mg QD for 13 days<br>Refractory Oropharyngeal Candidiasis:<br>400 mg BID<br>with a meal or with a nutritional supplement in patients who cannot tolerate a full meal |

## Table of Contents

## 1. Executive Summary

Posaconazole (POS, SCH 56592) is a triazole antifungal agent and, like other azoles such as fluconazole, itraconazole, and voriconazole, blocks ergosterol biosynthesis of yeast and filamentous fungi by inhibiting the enzyme lanosterol 14α-demethylase (CYP51, Erg11p). The drug formulation in this NDA is an oral suspension (40 mg/mL) and the proposed indications are prophylaxis [redacted] in patients, 13 years of age and older, who are at high risk of developing these infections, such as hematopoietic stem cell transplant (HSCT) recipients or those with prolonged neutropenia, and treatment of oropharyngeal candidiasis, including infections refractory to itraconazole and fluconazole. Priority review was granted for prophylaxis of [redacted].

The sponsor cross-referenced [redacted], for the clinical pharmacology information. All clinical pharmacology studies [redacted] have been previously reviewed by the FDA Clinical Pharmacology review team. Accordingly, most of the clinical pharmacology information to support the labeling of the current NDA 22-003 was based on the Clinical Pharmacology review of [redacted], dated May 24, 2005. In the Approvable letter, dated June 10, 2005, the sponsor was asked to address three unresolved clinical pharmacology issues regarding effect of severe hepatic impairment on the pharmacokinetics of POS and drug-drug interactions as pre-approval recommendations. However, none of these issues were addressed in the current NDA.

The efficacy and safety of posaconazole for the prophylaxis of IFIs were evaluated in two pivotal Phase 3 studies (Studies C98316 and P01899). These two pivotal Phase 3 study reports were reviewed to evaluate potential exposure-response relationships with POS.

The exposure-response analyses revealed a strong relationship between a higher incidence of Clinical Failure and lower plasma exposure to POS, suggesting that ensuring high plasma exposure to POS appears to be needed especially for patients whose steady state average concentration ($C_{avg}$) is low (see Figure 1). Further analyses showed:

(a) The exposure-response relationship for POS effectiveness for the prophylaxis against IFIs was not significantly confounded with any patient demographic covariates

(b) POS concentration of 350 ng/mL determined at 3 to 5 hours post dose on Day 2 after the beginning of POS treatment would result in a steady-state $C_{avg}$ of 700 ng/mL and subsequently result in the incidence of Clinical Failure of <25%. Plasma concentration monitoring of POS may be used as a tool to identify those patients who will have lower than desired plasma exposure.

(c) The increase of POS dose from 200 mg TID to 400 mg TID is most likely to result in an increase in plasma exposure to POS by at least 2 fold when POS is given either with food or under fasting conditions.

(d) There would be expected to be no additional safety findings with 400 mg TID for those patients whose $C_{avg}$ was ≤700 ng/mL (i.e., those who receive 200 mg TID initially). Based on the dose-proportional PK of POS, following 400 mg TID administration to patients whose $C_{avg}$ was ≤700 ng/mL (i.e., those who receive 200 mg TID initially), $C_{avg}$ would not be expected to be greater than 3650 ng/mL, which is the highest $C_{avg}$ observed in patients treated with 200 mg TID in Study C98316.

Collectively, it is recommended that POS dose be adjusted based on plasma concentrations of POS on Day 2.

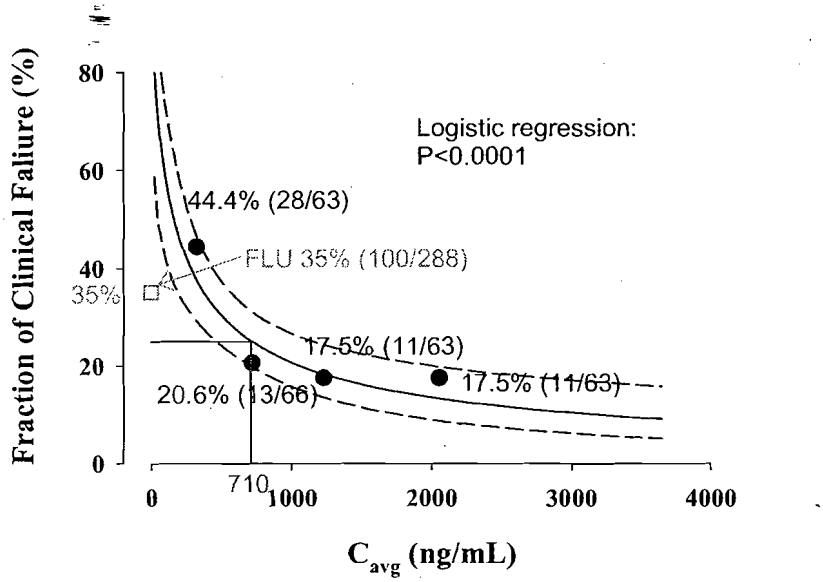



**Figure 1.** POS exposure-response relationship for patients in the All Treated population during the Primary Time Period (N=252) (Study C98316). Logistic regression was performed using natural log of average concentrations per patient ($log(C_{avg})$) as a continuous variable and the Clinical Failure as a binary variable (yes or no). The solid line represents the regression fit. The dashed lines represent 95% Confidence Interval. Subsequent to the logistic regression, the response rates in each of the 4 quartiles of $C_{avg}$ (closed circles) are plotted to assess the goodness-of-fit. The response rate for patients treated with fluconazole (FLU, open square) is plotted as a reference. The blue lines showed that 710 ng/mL of $C_{avg}$ is required to achieve 25% Clinical Failure rate.

### 1.1. Recommendation

It is strongly recommended to determine POS dose according to its plasma concentrations. The summary of dose adjustment, based on the monitoring of POS plasma concentrations, is illustrated as a flow chart below.

Initial dose: 200 mg TID for all patients

Monitoring of plasma concentration(s) of POS on Day 2:

Plasma samples should be collected at 3 to 5 hours after any dose on Day 2.

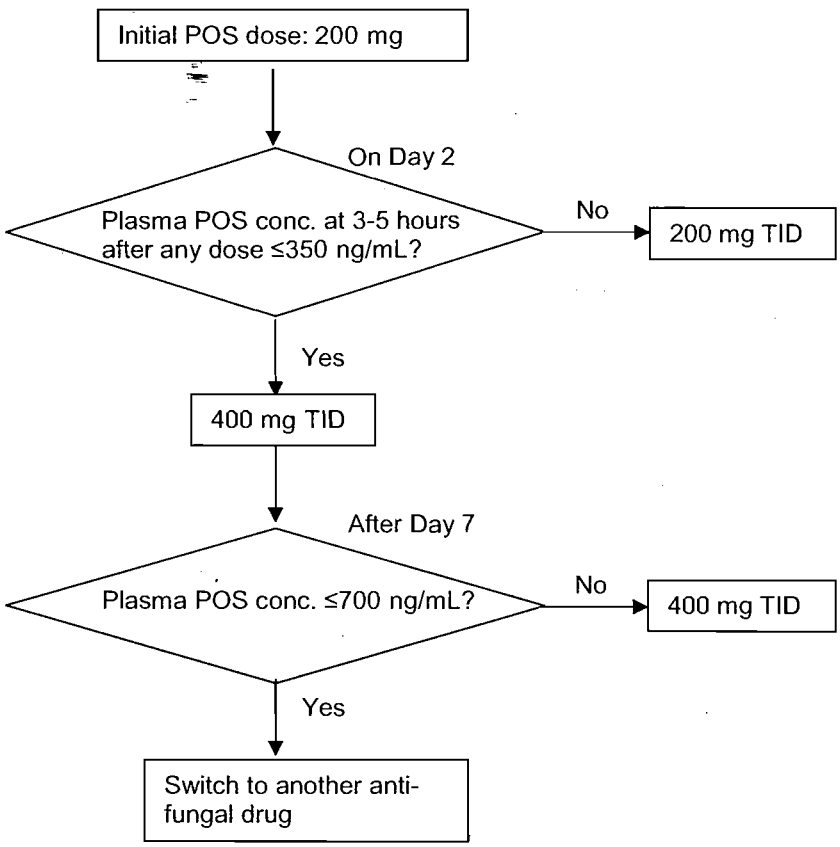
(a) If plasma concentration(s) of POS is ≤350 ng/mL, then give 400 mg TID

(b) If plasma concentration(s) of POS is >350 ng/mL, then give 200 mg TID

Monitoring of plasma concentration(s) of POS after Day 7 for patients who received 400 mg TID:

(a) If plasma concentration(s) of POS is >700 ng/mL, then give 400 mg TID

(b) If plasma concentration(s) of POS is ≤700 ng/mL, then switch to another anti-fungal drug




Scheme of POS Dose recommendation based on plasma concentrations of POS

## 1.2 Phase 4 Commitments

Not applicable.

Seong H. Jang, Ph.D.
Reviewer
Clinical Pharmacology
Pharmacometrics
DCP4/OCPB

Dakshina Chilukuri, Ph.D.
Reviewer
Pharmacometrics (Population PK)
DCP4/OCPB

Concurrence

Jogarao Gobburu, Ph.D.
Pharmacometrics Team Leader
OCP

Concurrence

Phil Colangelo, Pharm.D., Ph.D.
Team Leader
Clinical Pharmacology
DCP4/OCPB

## 1.3. Summary of Important Clinical Pharmacology Findings

**Exposure-response relationship-Effectiveness**

The exposure-response analyses revealed a strong relationship between a higher incidence of Clinical Failure and lower plasma exposure to POS, suggesting that ensuring high plasma exposure to POS appears to be needed especially for patients whose steady state average concentration ($C_{avg}$) is low (See Figure 1 on page 3). Table S1 shows the Clinical Failure rate and Proven/Probable IFIs in the All Treated population during the Primary Time Period for 4 quartiles of POS $C_{avg}$.

**Table S1.** Incidence of Clinical Failure and Proven/Probable IFIs in the All Treated population during the Primary Time Period in 4 quartiles of POS $C_{avg}$ (Study C98-316).

| Quartiles | Q1 | Q2 | Q3 | Q4 |
|---|---|---|---|---|
| **$C_{avg}$ (ng/mL)** | **21.5-557** | **557-915** | **915-1563** | **1563-3650** |
| **Clinical Failure** | **44.4% (28/63)** | **20.6% (13/63)** | **17.5% (11/63)** | **17.5% (11/63)** |
| Proven/probable IFI | 4.76% (3/63) | 4.76 % (3/63) | 1.59% (1/63) | 3.17% (2/63) |

**Dose recommendation based on the exposure-response relationship**

There are no patient demographic covariates (or combination of those covariates) that can successfully categorize the patients who will attain low plasma concentrations of POS. Therefore, measuring plasma concentrations of POS is considered by this reviewer to be the most reliable way to identify those patients who will attain low concentrations of POS.

Based on the relationship between $C_{avg}$ of POS and Clinical Failure (See Figure 1 on page 3), a Clinical Failure rate of <25% is considered to be acceptable by the reviewing medical officer as a target clinical outcome that should be achieved with POS and $C_{avg}$ should be greater than 700 ng/mL to achieve this target outcome. Thus, 700 ng/mL is the lower threshold value for $C_{avg}$ to determine if the POS dosage needs to be increased for a given patient. Subsequently, the concentration on Day 2 which would result in a $C_{avg}$ of 700 ng/ml at steady state was calculated using an accumulation factor of 8 obtained from a multiple dose-escalating PK study (Study I96089). Based on this, a concentration of 350 ng/mL measured at 3 to 5 hours post dose on Day 2 is recommended as a cutoff plasma concentration of POS to determine if the POS dosage needs to be increased for a given patient.

The threshold concentration of 700 ng/mL as $C_{avg}$ also appears appropriate in terms of the incidence of Proven/Probable IFIs, because the incidence of Proven/Probable IFIs also tended to be greater for patients whose $C_{avg}$ was ≤700 ng/mL compared with patients whose $C_{avg}$ was >700 ng/mL. Tables S2 and S3 shows the incidence of Prove/Probable IFIs between group of patients whose $C_{avg}$ was ≤700 ng/mL and group of patients whose $C_{avg}$ was >700 ng/mL in Study C98316 and P01899, respectively.

**Table S2.** Incidence of Proven/Probable IFIs between those patients whose POS $C_{avg}$ was ≤700 ng/mL and those patients whose POS $C_{avg}$ was >700 ng/mL (Study C98316).

| $C_{avg}$ (ng/mL) | ≤700 ng/mL (N=92) | >700 ng/mL (N=160) |
|---|---|---|
| Incidence of Prove/Probable IFIs | 6.52% (6/92) | 1.88% (3/160) |
| Incidence of Aspergillosis | 4.35% (4/92) | 0.63% (1/160) |

**Table S3.** Incidence of Proven/Probable IFIs between those patients whose $C_{avg}$ was ≤700 ng/mL and those patients whose $C_{avg}$ was >700 ng/mL (Study P01899).

| $C_{avg}$ (ng/mL) | ≤700 ng/mL (N=155) | >700 ng/mL (N=60) |
|---|---|---|
| Incidence of Prove/Probable IFIs | 3.87% (6/155) | 0% (0/60) |

Four clinical pharmacology studies (i.e., single and multiple dose escalating studies and food effect studies following 200 mg and 400 mg of POS) support that the increase of POS dose from 200 mg TID to 400 mg TID is most likely to result in an increase in plasma exposure to POS by at least 2 fold when POS is given either with food or under fasting conditions.

When dose is adjusted from 200 mg TID to 400 mg TID, based on the threshold $C_{avg}$ of 700 ng/mL, the percent of patients whose $C_{avg}$ is ≤700 ng/mL would be decreased from 37% (92/252) to 14% (35/252). The Clinical Failure rate for patients whose $C_{avg}$ was ≤700 ng/mL (i.e., with 200 mg TID) would be reduced from 37% (34/92) to 25% (23/92) (Table S4).

**Table S4.** Percent of patients whose $C_{avg}$ is ≤700 ng/mL and Clinical Failure rate as a function of POS dosing regimen

| $C_{avg}$ ≤700 ng/mL | 200 mg TID | 400 mg TID (projection) |
|---|---|---|
| % of patients whose $C_{avg}$ is ≤700 ng/mL | 37% (92/252) | 14% (35/252) |
| Clinical Failure rate in patients whose $C_{avg}$ was ≤700 ng/mL | 37% (34/92) | 25% (23/92) |

For patients whose plasma concentrations of POS cannot be high enough to ensure desirable clinical outcomes with 400 mg TID, other antifungal treatment for prophylaxis of IFIs may be needed. Thus, it is recommended to use other antifungal treatment instead of POS for patients who receive 400 mg TID and if plasma concentrations of POS after Day 7 (presumed steady state) are ≤700 ng/mL.

Collectively, the following dose administration and plasma concentration monitoring scheme is recommended by this reviewer.

Initial dose: 200 mg TID for all patients

Monitoring of plasma concentration(s) of POS on Day 2:

Plasma samples should be collected at 3 to 5 hours after any dose on Day 2.

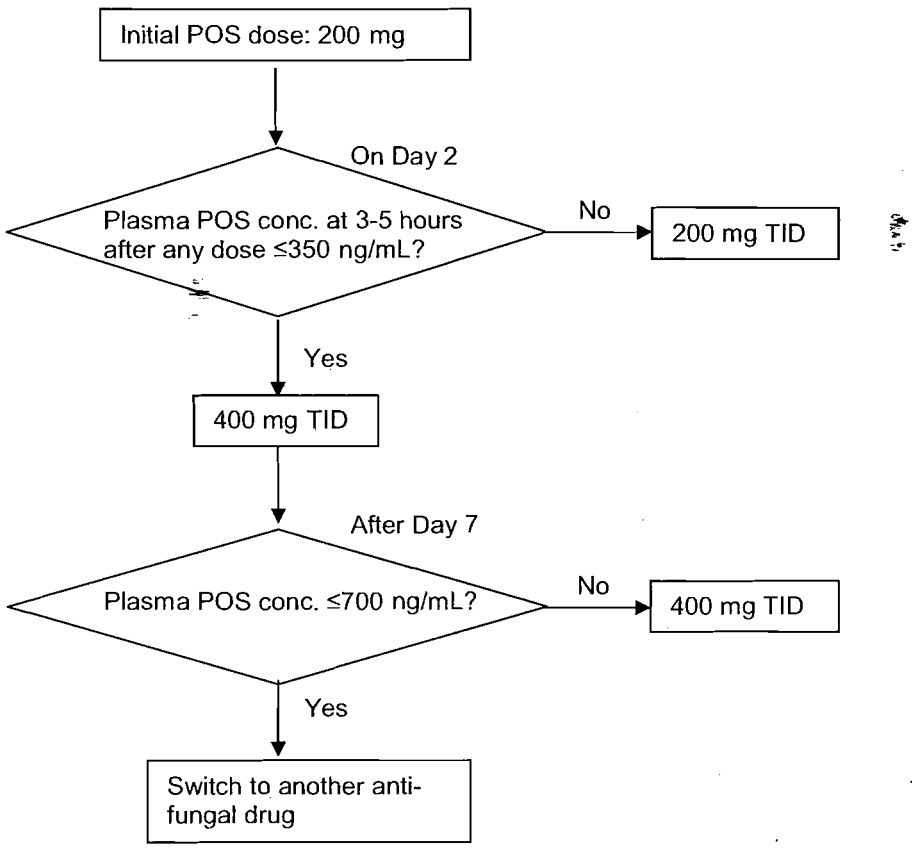
(a) If plasma concentration(s) of POS is ≤350 ng/mL, then give 400 mg TID

(b) If plasma concentration(s) of POS is >350 ng/mL, then give 200 mg TID

Monitoring of plasma concentration(s) of POS after Day 7 for patients who received 400 mg TID:

(a) If plasma concentration(s) of POS is >700 ng/mL, then give 400 mg TID

(b) If plasma concentration(s) of POS is ≤700 ng/mL, then switch to another anti-fungal drug




Scheme of POS Dose recommendation based on plasma concentrations of POS

**Exposure-response relationship-Safety**

The most common treatment-related (Possible and Probable) treatment-emergent adverse events were nausea, vomiting, diarrhea, hypokalemia, rash and elevations in hepatic enzymes (SGOT and SGPT increase). For exposure-response relationship regarding safety, data from Study C98316 and P01899 were pooled. Although the incidence of most treatment-related adverse events tended to be lower in the first quartile of $C_{avg}$ compared with the fourth quartile of $C_{avg}$, the incidence rates of adverse events were not significantly dependent on plasma drug concentration.

There would be expected to be no additional safety findings with 400 mg TID for those patients whose $C_{avg}$ was ≤700 ng/mL (i.e., those who receive 200 mg TID initially). Based on the dose-proportional PK of POS, following 400 mg TID administration to patients whose $C_{avg}$ was ≤700 ng/mL (i.e., those who receive 200 mg TID initially), $C_{avg}$

would not be expected to be greater than 3650 ng/mL, which is the highest $C_{avg}$ observed in patients treated with 200 mg TID in Study C98316.

## 2. Question Based Review

Exposure-response Analysis

The relationship between plasma exposure to posaconazole (POS) and its effectiveness and safety was analyzed by the FDA Clinical Pharmacology reviewer using data from two pivotal Phase 3 studies (Study C/I98-316 and P01899) which were conducted using POS for the prevention of IFIs in high-risk patients.

C98-316 was a double-blind, active-controlled trial, that compared POS (200 mg TID) with fluconazole (FLU, 400 mg QD) as prophylactic therapy to reduce the incidence of IFIs in high-risk allogeneic hematopoietic stem cell (HSCT) recipient with acute graft versus host disease (GVHD) or chronic GVHD. A total of 600 patients were enrolled (301 POS, 299 FLU). A Data Review Committee (DRC) of experts in antifungal therapy reviewed the blinded results of this study to make assessments of potential IFIs. The primary efficacy analysis was the DRC-adjudicated incidence of proven and probable IFI for All Randomized Subjects during the Primary Time Period (112-day fixed time period). The mean duration of therapy was comparable between the two treatment groups (80 days, POS; 77 days, fluconazole).

P01899 is a Phase 3, randomized, open-label, evaluator-blinded, active control, parallel group, multicenter study comparing POS (200 mg TID) versus standard azole (FLU 400 mg QD or itraconazole (ITZ) 200 mg BID) for prophylaxis against IFIs in subjects with profound, prolonged neutropenia due to remission-induction chemotherapy for AML or MDS. A total of 602 subjects were enrolled (304 POS, 298 standard azoles [240 FLU, 58 ITZ]). A blinded panel of external expert evaluators (DRC) reviewed all identified suspected cases of IFIs to determine the final number of proven, probable, and possible IFIs and to confirm the diagnosis (including the onset date of the infection and primary pathogen) based on EORTC/MSG criteria. The primary efficacy analysis was the DRC-adjudicated incidence of Proven/Probable IFIs in All Randomized Subjects during the Oral Treatment Phase (on-treatment period). The mean duration of therapy was comparable between the two treatment groups (29 days, POS; 25 days, fluconazole).

The primary efficacy variable specified in the protocol was not considered to be appropriate by the reviewing medical officer to evaluate efficacy of POS for prophylaxis against IFIs because the incidence of Proven or Probable IFIs are too rare to be compared. Thus, the FDA review team used Clinical Outcome as a primary endpoint to evaluate a treatment effect of POS regarding clinical failures for All Treated population defined as subjects who were randomized and received at least one dose of study drug. Clinical Failure was defined in the protocol as the occurrence of a proven or probable IFI, receipt of more than 5 days of empiric treatment with a systemic antifungal drug other than the study drug during the Primary Time Period, deaths from all causes, discontinuation of study drugs from the Primary Time Period (i.e., subject not followed for the entire duration of the period), or lost to follow up.

The exposure-relationship for safety was analyzed using the incidence of nausea, vomiting, diarrhea, elevations in hepatic enzymes (SGOT and SGPT increase or bilirubenemia), rash, and treatment discontinuation as the endpoints.

The exposure-response analysis for effectiveness and safety were evaluated by logistic regression which was performed using concentrations as a continuous variable and the clinical response or incidence of toxicity as a binary variable (yes or no). The SAS system for Windows V8 was used for the data manipulation and exposure-response analysis.

## 2.1. Exposure-response relationship-Effectiveness

### 2.1.1. Is posaconazole (POS) oral suspension, 200 mg TID, effective for the prophylaxis of invasive fungal infections (IFIs) in patients 13 years and older who are at high risk such as hematopoietic stem cell transplant recipients or those with prolonged neutropenia?

The efficacy of POS for prophylaxis against IFIs in patients who are at high risk such as hematopoietic stem cell transplant recipients (Study C98316) or those with prolonged neutropenia (P01899) was compared with the control group of subjects treated with fluconazole (FLU) and/or itraconazole (ITZ). The results based on the primary efficacy endpoint (i.e., Clinical Outcome) are summarized in Tables 1 and 2 (from Clinical Review from an FDA Medical Officer, Dr. Tierney Maureen). On the basis of Clinical Outcome, the results from Study C98316 supported noninferiority but not significant for superiority to the control group of subjects treated with FLU. On the other hand, the results from Study P01899 supported the superiority of POS to the control group of subjects treated with FLU and ITZ. Thus, collectively, POS is considered to be effective for the prophylaxis against IFIs in patients who are at high risk such as hematopoietic stem cell transplant recipients or those with prolonged neutropenia.

**Table 1.** Primary efficacy analysis for the prophylaxis against invasive fungal infections in high-risk allogeneic hematopoietic stem cell recipient with acute graft versus host disease (GVHD) or chronic GVHD. (Study C98316: All Treated Population).

| | POS | | Fluconazole | | P value | Difference | 95% CI |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | | | |
| Clinical Success | 202 | 69 | 188 | 65 | 0.29 | 4% | -3.5%, 11.7% |
| Clinical Failure | 89 | 31 | 100 | 35 | | | |
| Total | 291 | | 288 | | | | |

**Table 2.** Primary efficacy analysis for the prophylaxis against invasive fungal infections in subjects with profound, prolonged neutropenia. (Study P01899: All Treated Population).

| | POS | | Fluconazole | | P value | Difference | 95% CI |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | | | |
| Clinical Failure | 107 | 46 | 137 | 58 | 0.01 | 11.8% | 2.9%, 20.8% |
| Clinical Success | 127 | 54 | 101 | 42 | | | |
| Total | 234 | | 238 | | | | |

| | POS | | Itraconazole | | P value | Difference | 95% CI |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | | | |
| Clinical Failure | 37 | 59 | 37 | 69 | 0.27 | 9.8% | -7.5%, 27% |
| Clinical Success | 26 | 41 | 17 | 31 | | | |
| Total | 63 | | 54 | | | | |

### 2.1.2. Is the effectiveness of POS for the prophylaxis against IFIs dependent upon the plasma exposure to posaconazole?

This reviewer found that there is a strong relationship between a higher incidence of Clinical Failure and the lower plasma exposure to POS, suggesting that clinical response to POS is dependent upon its plasma concentrations.

The plasma POS concentrations were measured in 265 patients of total 291 patients in POS-treated arm. However, plasma POS concentrations were collected only at more than 24 hours after the last dose of POS in 13 patients of the 265 patients.. Thus, these 13 patients were excluded from the PK dataset (N=252). The Clinical Failure rate in the PK dataset (63/252=25%) was comparable with that in the All Treated Population (89/291=31%), indicating that the PK dataset represents All Treated Population adequately.

A total of 870 plasma samples were collected for the measurement of POS concentration from 252 patients at no later than 24 hours after the last dose of POS. An average of 3.5 POS concentrations per patient were determined and the individual average concentration values ($C_{avg}$) were used to relate the plasma exposure to POS and response. See **2.1.10** to find the rationale for the use of $C_{avg}$ as a PK parameter for the exposure-response analysis.

Figure 2 shows the exposure-effectiveness relationship of POS for prophylaxis of IFIs in hematopoietic stem cell transplant recipients (Study C98316). Table 3 shows the Clinical Failure rate in the All Treated population during the Primary Time Period for 4 quartiles of POS $C_{avg}$. Additionally, the reasons for Clinical Failure were analyzed for 4 quartiles of POS $C_{avg}$ (Table 3). The incidence of Proven/Probable IFIs tended to be greater in the lower two quartiles (i.e., Q1 and Q2) compared with the higher two quartiles (i.e., Q3 and Q4), but no statistical significance was observed between the incidence of Prove/Probable IFIs and POS $C_{avg}$ (p=0.3). The results showed that the major reason for Clinical Failure was death. The statistical results of logistic regression analysis, using the Clinical Failure

as the dependent binary variable (i.e., yes or no) and $C_{avg}$ as the independent continuous variable, are summarized in Table 4.

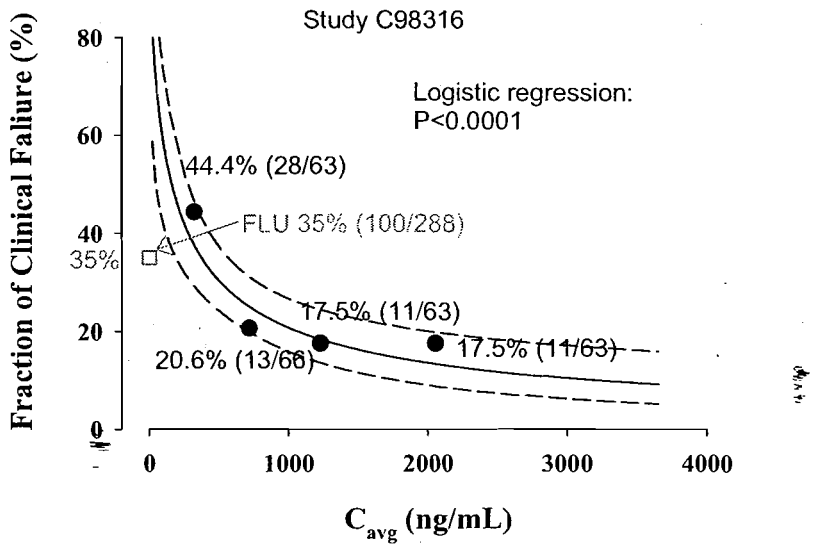



**Figure 2.** POS exposure-response relationship for patients in the All Treated population during the Primary Time Period (N=252) (Study C98-316). Logistic regression was performed using natural log of average concentrations per patient ($log(C_{avg})$) as a continuous variable and the Clinical Failure as a binary variable (yes or no). The solid line represents the regression fit. The dashed lines represent 95% Confidence Interval. Subsequent to the logistic regression, the response rates in each of the 4 quartiles of $C_{avg}$ (closed circles) are plotted to assess the goodness-of-fit. The response rate for patients treated with fluconazole (FLU, open square) is plotted as a reference.

**Table 3.** Incidence of Clinical Failure in the All Treated population during the Primary Time Period in 4 quartiles of POS $C_{avg}$ (Study C98-316).

| Quartiles | Q1 | Q2 | Q3 | Q4 |
|---|---|---|---|---|
| **$C_{avg}$ (ng/mL)** | **21.5-557** | **557-915** | **915-1563** | **1563-3650** |
| **Clinical Failure** | **44.4% (28/63)** | **20.6% (13/63)** | **17.5% (11/63)** | **17.5% (11/63)** |
| Proven/probable IFI | 4.76% (3/63) | 4.76 % (3/63) | 1.59% (1/63) | 3.17% (2/63) |
| Empirical use of Sys. Antifungal [a] | 17.5% (11/63) | 3.17% (2/63) | 6.35% (4/63) | 4.76% (3/63) |
| Death | 34.9% (22/63) | 20.6% (13/63) | 17.5% (11/63) | 11.1% (7/63) |
| Discontinuation [b] | 23.8% (15/63) | 14.3% (9/63) | 9.52% (6/63) | 9.52% (6/63) |

There is some overlap in the rows.
[a]: Use of systemic antifungal agents in addition to study drug more than 5 days, from all causes
[b]: Discontinuation due to any reason

**Table 4.** Parameter estimates of the logistic regression model for the relationship between log($C_{avg}$) and the Clinical Failure in the All Treated population during the Primary Time Period (Study C98-316).

| Parameter | | Estimate | SE | P-value |
|---|---|---|---|---|
| Clinical Failure | Intercept | 3.7466 | 1.0713 | 0.005 |
| | Slope | -0.7369 | 0.1634 | <0.0001 |

There was a significant difference in Clinical Failure rate between patients who belong to Q1 (i.e., $C_{avg}$ <557 ng/mL) and patients who belong to Q2- Q4 (i.e., $C_{avg}$ > 557 ng/mL), i.e., 44% (28/63) *vs.* 19% (35/189). Based on the results of this analysis, ensuring high plasma exposure to POS appears to be needed for patients whose $C_{avg}$ is low. It should be noted that the Clinical Failure rate for patients who belonged to Q1 was even higher compared with patients who received FLU (See Figure 2).

The same exposure-effectiveness analysis was performed using data from Study P01899. The similar results, i.e., a strong relationship between lower $C_{avg}$ of POS and higher Clinical Failure rate was obtained in subjects with profound, prolonged neutropenia due to remission-induction chemotherapy for AML or MDS (Figure 3 and Tables 5 and 6).

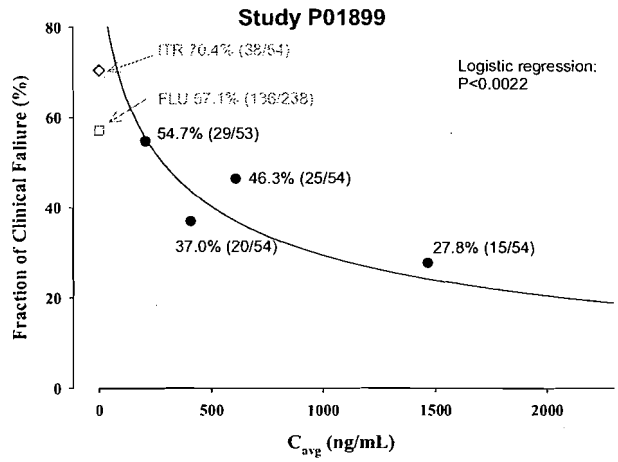



**Figure 3.** POS exposure-response relationship for patients in the All Treated population during the Oral Treatment Phase (n=215) (Study P01899). Logistic regression was performed using natural log of average concentrations per patient (log($C_{avg}$)) as a continuous variable and the Clinical Failure as a binary variable (yes or no). The solid line represents the regression fit. Subsequent to the logistic regression, the response rates in each of the 4 concentration quartiles (closed circles) are plotted to assess the goodness-of-fit. The response rates in patients treated with fluconazole (FLU, open square) and itraconazole (ITZ, open diamond) are plotted as references.

**Table 5.** Incidence of Clinical Failure and Proven/Probable IFIs in the All Treated population during the Oral Treatment Phase in 4 concentration quartiles of POS (Study P01899).

| $C_{avg}$ (ng/mL) | Clinical Failure | Proven/probable IFI |
|---|---|---|
| 89.65-322 | 54.7% (29/53) | 3.77% (2/53) |
| 322-490 | 37.0% (20/54) | 1.85 % (1/54) |
| 490-733.5 | 46.3% (25/54) | 5.56% (3/54) |
| 733.5-2200 | 27.8% (15/54) | 0% (0/54) |

**Table 6.** Parameter estimates of the logistic regression model for the relationship between log($C_{avg}$) and Clinical Failure in the All Treated population during the Oral Treatment Phase (Study P01899).

| Parameter | | Estimate | SE | P-value |
|---|---|---|---|---|
| Clinical Failure | Intercept | 3.9179 | 1.3969 | 0.005 |
| | Slope | -0.6938 | 0.2267 | 0.0022 |

As mentioned above, Study P01899 was designed as an open-label study. Additionally, the range of individual $C_{avg}$ values was observed to be wider in Study C-98-316 as compared with Study P01899. Thus, further exposure-effectiveness analyses were performed using data obtained from Study C98316.

### 2.1.3. Is the above exposure-effectiveness relationship confounded with any other patient demographic covariates?

The exposure-response relationship for POS effectiveness for the prophylaxis against IFIs was not significantly confounded with any patient demographic covariates.

The reviewer investigated if the exposure-effectiveness relationship was confounded with any patient characteristics. The analysis showed some trends such as (a) higher incidence of death in Q1, (b) shorter treatment duration in Q1, (c) less patients with Acute III GVHD at baseline in Q4, (d) more patients with Acute II GVHD at baseline in Q1, (e) less female patients in Q1, (f) more frequent incidence of diarrhea in Q1, and (g) more African-American patients in Q1 (Table 7). However, none of these covariates could identify the patients to all 4 quartiles as significantly as $C_{avg}$.

**Table 7.** Comparison of patient demographic covariates in All Treated population as a function of plasma POS concentration (Study C98-316: N=252).

| Quartile | Q1 (n=63) | Q2 (N=63) | Q3 (N=63) | Q4 (N=63) |
|---|---|---|---|---|
| $C_{avg}$ (ng/mL)[a] | 296±170<br>322<br>[22-549] | 740±102,<br>718<br>[565-913] | 1232±200,<br>1231<br>[917-1562] | 2146±492,<br>2056<br>[1563-3650] |
| Death | 22 | 13 | 12 | 7 |
| Tx Duration (Days) | 69.2±44.6 | 92.2±32.5 | 101±26.4 | 91.0±37.3 |
| GVHDBS | | | | |
| Acute II or Chronic Extensive | 77.8% | 68.2% | 82.5% | 85.7% |
| Acute III | 17.5% | 23.8% | 14.3% | 7.94% |
| Acute IV | 3.17% | 3.17% | 3.17% | 3.17% |
| Acute II | 60.3% | 46.7% | 47.6% | 28.6% |
| Extensive | 17.5% | 22.6% | 34.9% | 57.1% |
| Gender (female) | 20.6% | 33.3% | 36.5% | 34.9% |
| Age (years) | 40±13 | 41±10 | 43±11 | 45±11 |
| Diarrhea [b] | 14.3% | 6.35% | 4.76% | 3.17% |
| Vomit [b] | 3.17% | 6.15% | 1.59% | 4.76% |
| Race (Cauc.) | 85.7% | 81.0% | 87.3% | 84.1% |
| Race (AA) | 9.52% | 6.35% | 0% | 0% |

[a]: Mean±SD, median [range] [b]: incidence on the day of plasma sample

The major reason for the shorter duration of therapy in Q1 was the greater incidence of death in Q1. As mentioned in **2.1.2**, death is the major reason for Clinical Failure. Thus, a short duration of therapy in Q1 was most likely to be an effect of low plasma exposure to POS but not a cause for low plasma exposure to POS. The Clinical Failure rate for African-American patients was 20% (2/10), indicating more African-American patients in Q1 was not confounded with exposure-effectiveness relationship of POS. Although the incidence of diarrhea appears to be related to low plasma exposure to POS, only 14% of patients who belong to Q1 had diarrhea. Thus, it is not likely to be a major reason for low plasma exposure to POS.

After discussion of this analysis with the sponsor on May 26, 2006, the sponsor identified three risk factors (i.e., Acute GVHD at baseline, male, and CMV positive) which were strongly correlated with Clinical Failure using a logistic regression analysis (backward selection). The sponsor defined a sub population of patients with the three identified risk factors named above (n=51) and showed that there were relatively more patients (46%) who belonged to Q1 in this "high risk" sub population. However, the further exposure-response analysis performed by the Clinical Pharmacology reviewer showed that the Clinical Failure rate is greater in patients who belonged to Q1 compared with Q2-Q4 within the "high risk" sub population group. In addition, an almost identical exposure-effectiveness relationship was observed within a sub population which excluded the high risk sub population (N=240), indicating that the exposure-response relationship for POS effectiveness for the prophylaxis against IFIs was not confounded with any patient demographic covariates (See Appendix ).

### 2.1.4. Is there any way to identify the patients who attain low plasma concentrations of POS?

Measuring POS plasma concentration is considered by this reviewer to be the most reliable way to identify patients who attain low plasma concentrations of POS.

As discussed in **2.1.3**, there are no patient demographic covariates (any combination of those covariates) that can successfully identify the patients who will attain low plasma concentrations of POS. Therefore, measuring plasma concentration is considered to be the most reliable way to identify patients who will attain low plasma concentrations of POS. Currently, the sponsor does not have a commercial assay method to monitor plasma concentrations of POS. Thus, it is recommended that the sponsor develop a commercial assay method to monitor plasma concentrations of POS.

### 2.1.5. What will be the cutoff or threshold concentration of POS to determine if a patient needs an increase in the POS dosage?

It is recommended to use a POS plasma concentration of 350 ng/mL measured at 3 to 5 hours post dose on Day 2 as a cutoff plasma concentration of POS.

This is based on the relationship between $C_{avg}$ of POS and Clinical Failure (See Figure 2 on page 13). A Clinical Failure rate of <25% is considered by the reviewing medical officer to be acceptable as a target clinical outcome. Figure 1 on page 13 shows that $C_{avg}$ should be greater than 700 ng/mL to achieve this target outcome. Thus, 700 ng/mL is the lower threshold value for $C_{avg}$ at steady state to determine if the POS dosage needs to be increased for a given patient.

POS PK can be described appropriately by a one compartment open model with a first order rate of absorption and a first order rate of elimination (See Section **5.** Population PK analysis). Thus, the plasma concentrations of POS before it reaches a steady state (i.e., during the first week after the beginning of POS treatment) could be calculated from steady state plasma concentrations using an accumulation factor of 8 obtained from a multiple dose-escalating PK study (Study I96089). Table 8 shows that the calculated average plasma concentrations of POS before $C_{avg}$ reaches 700 ng/mL at Day 7 (presumed steady state) following oral administration of POS 200 mg TID.

**Table 12.** Calculated plasma concentrations of POS before $C_{avg}$ reaches 700 ng/mL at Day 7 (presumed at steady state) following oral administration of POS 200 mg TID.

| Day | No. of Dose | Plasma concentration of POS (ng/mL) |
|---|---|---|
| 1 | 1 | 67 |
| | 2 | 186 |
| | 3 | 238 |
| 2 | 4 | 286 |
| | 5 | 331 |
| | 6 | 371 |
| 3 | 7 | 408 |
| | 8 | 442 |
| | 9 | 474 |
| 4 | 10 | 503 |
| | 11 | 529 |
| | 12 | 553 |
| 5 | 13 | 576 |
| | 14 | 596 |
| | 15 | 615 |
| 6 | 16 | 632 |
| | 17 | 648 |
| | 18 | 663 |
| 7 | 19 | 676 |
| | 20 | 689 |
| | 21 | 700 |

For the calculation, 7.6±2.8 of accumulation ratio ($R_{0\text{-}12h}$) obtained following oral administration of POS 200 mg BID for 14 days (Study 196089) were used.

Based on the above results, a POS plasma concentration of 350 ng/mL measured at 3 to 5 hours post dose on Day 2 is recommended as a cutoff plasma concentration of POS to determine if the POS dosage needs to be increased for a given patients.

For Day 1, plasma concentrations of POS vary substantially. Thus, the plasma concentrations of POS on Day 1 are not recommended to be used as criteria to predict $C_{avg}$ at steady state. It should be noted that plasma concentrations of POS should be measured at 3 to 5 hours after each dose considering median value of $T_{max}$, 3 hour.

### 2.1.6. How can plasma concentrations of POS be increased in patients who cannot achieve high plasma exposure to POS (i.e., patients who belongs to Q1)?

The increase of POS dose from 200 mg TID to 400 mg TID is most likely to result in an an increase in plasma exposure to POS by at least 2 fold when POS is given either with food or under fasting conditions.

The reviewer recommends that POS dose regimen be adjusted to 400 mg TID from 200 mg TID for patients whose plasma concentrations of POS need to be increased. This

recommendation is based on the following results obtained from clinical pharmacology studies conducted in healthy subjects

).

A multiple dose escalating study (Study I96089) showed that 400 mg BID dose resulted in 2.3-fold increase in plasma exposure to POS (i.e., AUC and $C_{max}$) compared with 200 mg BID dose when it is given with a high-fat meal (Table 9). A single dose escalating study (Study I95098) also showed that a single dose of 400 mg POS resulted in about 2-fold increase in both AUC and $C_{max}$ compared with a single dose of 200 mg POS dose when it given with a high-fat meal (Table 10). No dose escalating study was conducted under fasting conditions. However, two studies to evaluate the effect of food on the POS PK (Studies I96099 and I95099) showed that the magnitude of the increase in oral POS bioavailability by a high-fat meal was similar (i.e., ~4 fold) following oral administration of both 200 mg and 400 mg (Tables 11 and 12). Collectively, these data support that 400 mg dose can increase plasma exposure to POS by at least 2-fold compared with 200 mg dose when POS is given under fasting conditions as well as when it is given with a high-fat meal. Thus, the increase of POS dose from 200 mg TID to 400 mg TID is most likely to result in an increase in plasma exposure to POS by at least 2 fold when POS is given either with food or under fasting conditions.

**Table 9.** Pharmacokinetic parameters (Mean±SD [range]) of POS tablets on Day 14 after oral (Q12 hr) administration of POS tablets for 14 days (n=9/Dose)
(Study I96-089)

| | 200 mg BID | 400 mg BID | Fold Difference |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 1753±466 [1020-2230] | 4150±816 [2920-5710] | 2.37 |
| $AUC_{0-12}$ (ng·hr/mL) | 16801±4319 [8929-21960] | 39206±8020 [24475-47985] | 2.33 |

**Table 10.** Pharmacokinetic parameters (Mean±SD [range]) of POS following single oral administration of POS tablets to healthy male volunteers (n=6 for each dose). (Study I95-098)

| | 200 mg | 400 mg | Fold Difference |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 332±70.8 [273-470] | 611±190 [424-964] | 1.84 |
| $AUC_{inf}$ (ng·hr/mL) | 10896±3411 [5650-14634] | 20264±6781 [12716-29387] | 1.86 |

**Table 11.** Pharmacokinetic parameters (Mean±SD [range]) of POS (n=20) after a single oral administration of 400 mg oral suspension after a 10-hr fast or a high-fat breakfast (Study I96099)

| | Suspension (fasted) | Suspension (high-fat meal) | Fold Difference |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 132±65.8 [45.7-267] | 512±176 [241-1016] | 3.88 |
| $AUC_{inf}$ (ng·hr/mL) | 4179±1285 [2705-7269] | 13885±5655 [7854-34824] | 3.3 |

**Table 12.** Pharmacokinetic parameters (Mean (CV%)) of POS (n=20) after a single oral administration of 200 mg oral capsule after a 10-hr fast or a high-fat breakfast (Study I95099)

| | Capsules (fasted) | Capsules (high-fat meal) | Fold Difference |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 102.3 (39%) | 531.4 (32%) | 5.2 |
| $AUC_{inf}$ (ng·hr/mL) | 3588 (37%) | 14293 (38%) | 3.98 |

. Briefly, the oral absorption of POS is dose-limited presumably due to low solubility of POS in aqueous and acidic media and significantly dependent upon food intake. The plasma exposure to POS after a single dose administration is increased by about 2.6-fold when given with a non fat meal (~14g fat) or a nutrient supplement (Boost Plus®: ~14 g fat) and by about 4-fold when given with a high-fat meal (~50 g fat). In fasted healthy subjects, the bioavailability of a total daily dose of POS 800 mg was increased by 80% when the dose was administered as 200 mg QID compared with when the dose administered as 400 mg BID.

One way to enhance the oral absorption of POS is to administer POS oral suspension with a nutritional supplement in patients who cannot tolerate a full meal. According to the study protocol, however, POS oral suspension should be administered with food and, therefore, administering POS with food appears to have been attempted as much as possible in the Study. In addition, as discussed in **2.1.3**, the baseline disease sickness, which may represent patient status for food intake, did not correlate significantly with plasma exposure to POS. Thus, administering POS with a meal or a nutritional supplement does not appear to be a practically feasible way to increase plasma exposure to POS for patients whose plasma concentrations of POS need to be increased, because those patients may already take POS with food or liquid nutritional supplement, or because those patients may not be able to be tolerate either food or oral liquid supplement.

An increase in the frequency of dosing, such as 200 mg QID, may be another way to increase plasma exposure to POS. However, QID dosing regimen is not likely to be preferred to TID dosing regimen in terms of coincidence of the timing of meals and compliance.

### 2.1.7. Is it appropriate to use Clinical Failure, instead of the incidence of Proven/Probable IFIs, for the determination of the cutoff concentration of POS to identify out the patients whose plasma concentrations of POS need to be increased?

It appears appropriate to use Clinical Failure as an end point to determine dose recommendation because the incidence of Proven/Probable IFIs also tended to be greater for patients whose $C_{avg}$ was ≤700 ng/mL compared with patients whose $C_{avg}$ was >700 ng/mL.

As mentioned above, the primary efficacy endpoint specified in the protocol was the incidence of Proven or Probable IFIs. However, since the study was designed to evaluate the efficacy of POS for the prophylaxis against IFIs, the FDA Medical Officers and Statistical reviewers considered that the incidence of Proven/probable IFIs per se is not appropriate to evaluate the efficacy of POS for the prophylaxis against IFIs. In addition, the incidence of Proven/Probable IFIs was too rare to be compared with statistical significance. Thus, Clinical Failure which associated with several factors (See **2.** on page 10) was used as a primary end point to evaluate the efficacy of POS for prophylaxis against IFIs. The analysis using Clinical Failure as a primary end point supported the non-inferiority of POS compared with the control group (fluconazole) with statistical significance as the analysis using the incidence of Proven/Probable IFIs as an end point did. Similarly, the use of Clinical Failure for the recommendation of POS dose and administration should be validated in terms of the incidence of Proven/Probable IFIs.

As discussed in **2.1.2**, the relationship between the incidence of Proven/Probable IFIs and $C_{avg}$ of POS was not significantly significant (p=0.3; logistic regression), but the relationship between Clinical Failure and $C_{avg}$ of POS was (P<0.0001). This may be due to the insufficient number of incidence of Proven/Probable IFIs to have statistical significance. Due to the same reason, there was no substantial difference in the incidence of Proven/Probable IFIs for 4 quartiles of POS $C_{avg}$ (See Table 3 on page 13). Thus, alternatively, the incidence of Proven/Probable IFIs was compared between Q1-Q2 and Q3-Q4. Table 13 shows POS $C_{avg}$ in patients who had Proven/Probable IFIs and Table 14 shows that the incidence of Proven/Probable IFIs and Aspergillus infection in Q1-Q2 vs. Q3-Q4. The results support that a higher incidence of Proven/Probable IFIs is most like to be related with lower plasma exposure to POS.

**Table 13.** POS $C_{avg}$ in patients who has Proven/Probable IFIs (Study C98316)

| Subject ID | $C_{avg}$ (ng/mL) | Quartile | Pathogen |
|---|---|---|---|
| 1004000048 | 99 | Q1 | Aspergillosis |
| 1004000049 | 158 | Q1 | Aspergillosis |
| 1004000050 | 319 | Q1 | Candidiasis |
| 1004000051 | 565 | Q2 | Aspergillosis |
| 1004000052 | 681 | Q2 | Aspergillosis |
| 1004000053 | 691 | Q2 | Other Fungi |
| 1004000054 | 1562 | Q3 | Aspergillosis |
| 1004000055 | 2080 | Q4 | Candidiasis |

| | | | |
|---|---|---|---|
| I004000056 | 2190 | Q4 | Other fungi |

**Table 14.** Incidence of Proven/Probable IFIs in Q1-Q2 vs. Q3-Q4 (Study C98316).

| | Q1-Q2 (N=126) | Q3-Q4 (N=126) |
|---|---|---|
| $C_{avg}$ (ng/mL) | 21.5-915 | 915-3650 |
| Incidence of Prove/Probable IFIs | 4.76% (6/126) | 2.38% (3/126) |
| Incidence of Aspergillosis | 3.17% (4/126) | 0.79% (1/126) |

Further analysis, more importantly, showed that the incidence of Proven/Probable IFIs and Aspergillus infection in patients whose POS $C_{avg}$ is ≤700 ng/mL were substantially higher compared with patients whose POS $C_{avg}$ is >700 ng/mL (Table 15). The results support the use of Clinical Failure for the recommendation of POS dose and validate the threshold plasma concentration of 700 ng/mL as $C_{avg}$ in terms of the incidence of Proven/Probable IFIs.

**Table 15.** Incidence of Proven/Probable IFIs between those patients whose POS $C_{avg}$ is ≤700 ng/mL and those patients whose POS $C_{avg}$ is >700 ng/mL (Study C98316).

| $C_{avg}$ (ng/mL) | ≤700 ng/mL (N=92) | >700 ng/mL (N=160) |
|---|---|---|
| Incidence of Prove/Probable IFIs | 6.52% (6/92) | 1.88% (3/160) |
| Incidence of Aspergillosis | 4.35% (4/92) | 0.63% (1/160) |

In this analysis, 4 patients who had Proven/Probable IFIs were excluded because their plasma concentrations were measured only at more than 2 days after the last dose of POS. PK samples were collected at three days after the last dose of POS in 2 patients and at 14 days in 1 patient, and no information regarding PK sample day was provided in 1 patient. In the two patients whose PK samples were collected at three days after the last dose of POS, $C_{avg}$ could be predicted using a mean $T_{1/2}$ (35 hours, range 20 to 66 hours). Based on the predicted $C_{avg}$ values (approximately 54 ng/mL and 388 ng/mL), these two patients obviously belong to Q1. Including these two patients for the analysis, the incidence rate of Proven/Probable IFIs would be 7.5% (5/65) in Q1, 6.34% (8/126) in Q1-Q2, and 8.7% (8/92) in patients whose $C_{avg}$ ≤700 ng/mL, supporting the significant relationship between a higher incidence of Proven/Probable IFIs and lower plasma concentrations of POS.

The data obtained from Study P01899 also support the cutoff concentration of 700 ng/mL as $C_{avg}$ to identify the patients who need an increase in POS dosage to attain a higher plasma concentration of POS. Compared with Study C98316, the plasma concentrations of POS were relatively lower in Study P01899 (See Table 5 on page 15). Table 16 shows POS $C_{avg}$ in patients who had Proven/Probable IFIs and Table 17 shows that the incidence of Proven/Probable IFIs between those patients whose POS $C_{avg}$ is ≤700 ng/mL and those patients whose POS $C_{avg}$ is >700 ng/mL. No incidence of Prove/Probable IFIs in patients who belong to Q4 and all Proven/Probable IFIs occurred for patients whose $C_{avg}$ was ≤700 ng/mL. These results support again the use of Clinical Failure for the recommendation of POS dose and validate the threshold plasma concentration of 700 ng/mL as $C_{avg}$ in terms of the incidence of Proven/Probable IFIs.

**Table 16.** POS $C_{avg}$ in patients who had Proven/Probable IFIs (Study P01899)

| Subject ID | $C_{avg}$ (ng/mL) | Quartile | Pathogen |
|---|---|---|---|
| 0054001468 | 254 | Q1 | Aspergillosis |
| 0010001371 | 294 | Q1 | Other Fungi |
| 0015001239 | 417 | Q2 | Aspergillosis |
| 0015001415 | 491 | Q3 | Candidiasis |
| 0057001492 | 606 | Q3 | Candidiasis |
| 0002001271 | 629 | Q3 | Other Fungi |

**Table 17.** Incidence of Proven/Probable IFIs between those patients whose POS $C_{avg}$ is ≤700 ng/mL and those patients whose POS $C_{avg}$ is >700 ng/mL (Study P01899).

| $C_{avg}$ (ng/mL) | ≤700 ng/mL (N=155) | >700 ng/mL (N=60) |
|---|---|---|
| Incidence of Prove/Probable IFIs | 3.87% (6/155) | 0% (0/60) |

Collectively, it is not inappropriate to use Clinical Failure, instead of Proven/Probable IFIs, for the determination of the cutoff concentration of POS to identify the patients who needs an increase in the POS dosage. Additionally, the threshold concentration of 700 ng/mLas $C_{avg}$ appears appropriate in terms of the incidence of Proven/Probable IFIs as well as in terms of Clinical Failure.

### 2.1.8. What will be the therapeutic advantage when POS dose is adjusted based on plasma concentrations of POS?

When dose is adjusted from 200 mg TID to 400 mg TID, based on the threshold $C_{avg}$ of 700 ng/mL, the percent of patients whose $C_{avg}$ is ≤700 ng/mL would be decreased from 37% (92/252) to 14% (35/252). The Clinical Failure rate for patients whose $C_{avg}$ was ≤700 ng/mL (i.e., with 200 mg TID) would be reduced from 37% (34/92) to 25% (23/92) (Table 18).

According to the POS concentration-Clinical Failure relationship (See **2.1.2**), in PK dataset from Study C98316, 37% total patients (92/252) has ≤700 ng/mL of $C_{avg}$ which resulted in a Clinical Failure rate of >25%. When these patients receive 400 mg TID instead of 200 mg TID, plasma concentrations of POS is expected to be increased by at least 2 fold either under fasting conditions or when it given with food or a nutritional supplement (See **2.1.6**). Accordingly, when dose is adjusted from 200 mg TID to 400 mg TID based on the threshold $C_{avg}$ of 700 ng/mL, the percent of patients whose $C_{avg}$ is ≤700 ng/mL can be decreased from 37% (92/252) to 14% (35/252) (Table 18).

The therapeutic advantage can also be found in terms of the incidence of Clinical Failure. In PK dataset of Study C98316, the incidence of Clinical Failure was significantly different for patients whose $C_{avg}$ was >700 ng/ml (18%; 29/160) from patients whose $C_{avg}$ was ≤ 700 ng/mL (37%; 34/92). Based on these Clinical Failure rates, when dose adjusted from 200 mg TID to 400 mg TID, Clinical Failure rate for patients whose $C_{avg}$ was ≤700 ng/mL (i.e., with 200 mg TID) can be reduced from 37% to 25% (23(=57x0.18+35x0.37)/92).

**Table 18.** Percent of patients whose $C_{avg}$ is ≤700 ng/mL and Clinical Failure rate as a function of POS dosing regimen

| $C_{avg}$ ≤700 ng/mL | 200 mg TID | 400 mg TID (projection) |
|---|---|---|
| % of patients whose $C_{avg}$ is ≤700 ng/mL | 37% (92/252) | 14% (35/252) |
| Clinical Failure rate in patients whose $C_{avg}$ is ≤700 ng/mL | 37% (34/92) | 25% (23/92) |

### 2.1.9. What dosage(s) are recommended based on the exposure-effectiveness relationship?

Based on the results of the above analyses, it is strongly recommended to determine POS dose according to its plasma concentration. The summary of dose recommendation based on the monitoring of POS plasma concentration is as follows.

Initial dose: 200 mg TID for all patients

Monitoring of plasma concentration(s) of POS on Day 2:

Plasma samples should be collected at 3 to 5 hours after any dose on Day 2.

(a) If plasma concentration(s) of POS is ≤350 ng/mL, then give 400 mg TID

(b) If plasma concentration(s) of POS is >350 ng/mL, then give 200 mg TID

For patients whose plasma concentrations of POS cannot be high enough to ensure desirable clinical outcomes with 400 mg TID, other antifungal treatment for prophylaxis of IFIs may be needed. Thus, it is recommended to measure additional plasma concentrations of POS for patients who received 400 mg TID after Day 7 when plasma concentrations of POS reach steady sate, and to switch to another antifungal treatment if $C_{avg}$ after Day 7 is ≤700 ng/mL. Accordingly, the subsequent dose recommendation for patients who receive POS 400 mg TID is as follows.

Monitoring of plasma concentration(s) of POS after Day 7 for patients who received 400 mg TID:

(a) If plasma concentration(s) of POS is >700 ng/mL, then give 400 mg TID

(b) If plasma concentration(s) of POS is ≤700 ng/mL, then switch to another antifungal drug

Figure 4 represents the scheme of dose recommendation of POS based on plasma concentrations of Posaconazole.

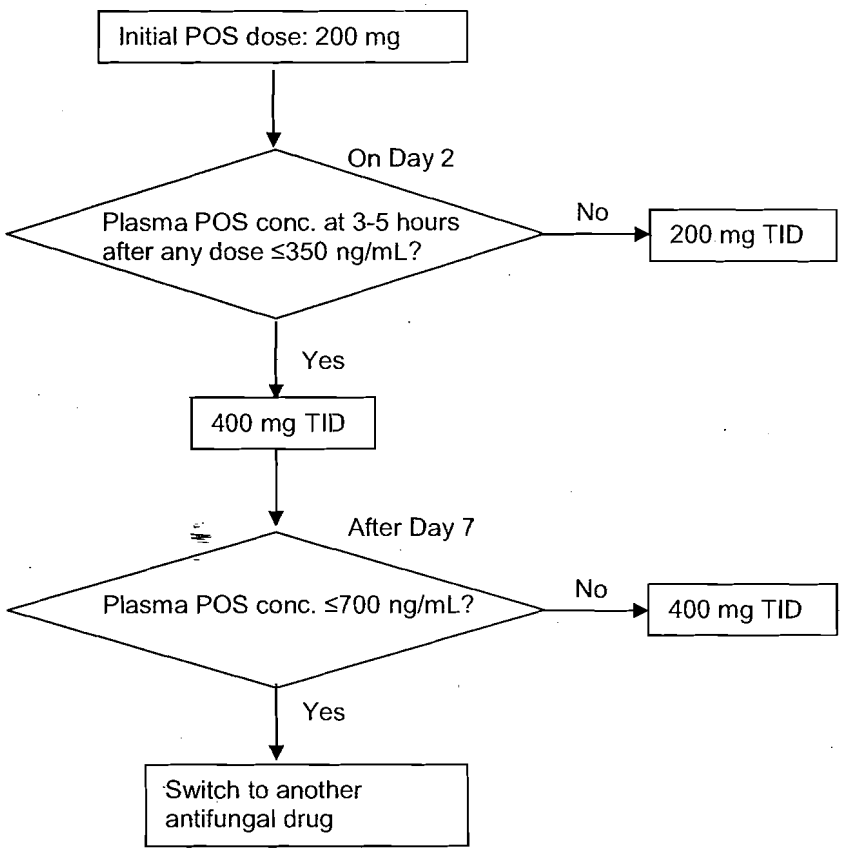



**Figure 4.** Dose recommendation of POS based on plasma concentrations of Posaconazole

**2.1.10. What PK parameter was used for exposure-response relationship?**

Individual subject's average concentration values ($C_{avg}$) were used to evaluate the exposure against response.

Since the elimination of POS is very slow (i.e., $T_{1/2}$: ~35 hours), the steady-state plasma concentration profile is relatively flat with minimal fluctuation over a dosing interval ). Thus, individual average concentration values ($C_{avg}$) were used to evaluate the exposure against response. Figure 5 shows POS concentrations measured in all patients and patients who belonged in Q1 in Study C98316 as a function of time (days) after the beginning of POS treatment. The plasma concentrations of POS in patients who belong in Q1 were relatively low throughout the study period, indicating that $C_{avg}$ in individual patient can be a PK parameter representing plasma exposure to POS.

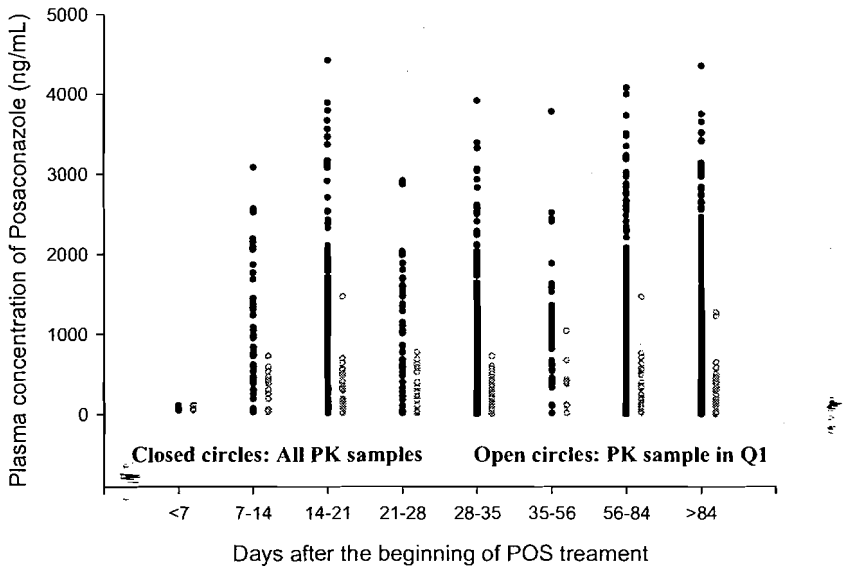



**Figure 5**. Plasma concentrations of POS (PK sample number=870) in all patients (n=252) as a function of time (days) after the beginning of POS treatment. (Study C98316)

## 2.2. Exposure-response relationship-Safety

### 2.2.1. What are the characteristics of the exposure-response relationship for safety?

The incidence rates of adverse events were not significantly dependent on plasma concentrations of POS.

The most common treatment-related (Possible and Probable) treatment-emergent adverse events were nausea, vomiting, diarrhea, hypokalemia, rash and elevations in hepatic enzymes (SGOT and SGPT increase). The relationship between these safety variables versus average plasma concentrations of POS ($C_{avg}$) were evaluated using a logistic regression analysis. In addition, the incidence rates of those adverse events were compared in 4 quartiles of $C_{avg}$. For these analyses, data from Study C98316 and P01899 were pooled. Plasma concentrations of POS were available from 450 patients of total 605 patients who received POS. The results are summarized in Table 19. Although the incidence of most treatment-related adverse events tends to be lower in the first quartile of $C_{avg}$ compared with the fourth quartile of $C_{avg}$, the incidence rates of adverse events were not significantly dependent on plasma drug concentration.

**Table 19.** Incidence of treatment-emergent and drug-related (Possible and Probable) AEs (%) in the All Treated population in 4 quartiles of average plasma concentration POS ($C_{avg}$) (N=450; Studies C98-316 and P01988). Datasets from Study C98-316 and P01899 were pooled for these analyses.

| | 1st Q (n=119) | 2nd Q (N=121) | 3rd Q (N=120) | 4th Q (N=120) | P value[b] |
|---|---|---|---|---|---|
| $C_{avg}$ (ng/mL)[a] | 205±105 [2.51-355] | 498±77.1 [355-626] | 835±138 [626-1118] | 1751±538 [1118-3650] | |
| Diarrhea | 3.36% | 4.96% | 8.33% | 6.67% | 0.4378 |
| Nausea | 7.56% | 6.61% | 10% | 12.5% | 0.3746 |
| Vomiting | 3.36% | 4.96% | 7.5% | 6.67% | 0.4639 |
| Discontinuation | 8.4% | 7.44% | 14.2% | 17.5% | 0.0595 |
| Bilirubinemia | 1.68% | 3.31% | 4.17% | 3.33% | 0.4787 |
| SGOT increased | 1.68% | 2.48% | 4.17% | 3.33% | 0.4016 |
| SGPT increased | 1.68% | 3.31% | 5% | 3.33% | 0.4911 |
| Hepatic enz. increased | 1.68% | 3.31% | 4.17% | 3.33% | 0.4787 |
| Hypokalemia | 0.84% | 1.65% | 4.17% | 2.5% | 0.4818 |
| Rash | 0.84% | 1.65% | 4.17% | 3.33% | 0.1739 |

[a]: Mean±SD [range]

[b]: Logistic regression for the relationship between the incidence of treatment-related adverse events and $C_{avg}$

### 2.2.2. Is there any expected safety issues when POS 400 mg TID is given to the patients whose steady-state $C_{avg}$ is ≤700 ng/mL?

There would be expected to be no additional safety findings with 400 mg TID for those patients whose $C_{avg}$ was ≤700 ng/mL (i.e., those who receive 200 mg TID initially). Based on the dose-proportional PK of POS, following 400 mg TID administration to patients whose $C_{avg}$ was ≤700 ng/mL (i.e., those who receive 200 mg TID initially), $C_{avg}$ would not be expected to be greater than 3650 ng/mL, which is the highest $C_{avg}$ observed in patients treated with 200 mg TID in Study C98316.

30 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Clin Pharm/Bio-_____*

## 4.2. Population PK analysis

### Objective of the analysis

To develop and validate a population pharmacokinetics model in the target population in order to find the influential covariates.

### Methods

### Design

This was a randomized, open-label, evaluator blinded, active-controlled, parallel-group, multicenter study. The study was designed to evaluate the safety and efficacy of posaconazole oral suspension compared with fluconazole or itraconazole in the prevention of invasive fungal infections in subjects with prolonged neutropenia due to remission induction chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes.

*Data:*

### Pharmacokinetics

In the Posaconazole group (POS), 215 patients had at least one POS plasma concentration measurement. A total of 702 plasma POS samples were used in this analysis

*Models*

### Pharmacokinetics

### Structural Model

All patients with available pharmacokinetic data in the POS group were included. Time post dose was calculated using the time and date information of the sampling time. Dosing times were assumed to be the nominal dosing times planned in the clinical study protocol. The number of doses taken by each patient was calculated using the TID dosing regimen and the number of days each patient was on POS therapy. Advan's 2, 5, and 7 in NonMem were investigated. Advan 2 (Oral one compartment model) with microconstants (Trans 2) was used.

### Covariate Model

Several subject covariates were available: gender, age, race, baseline body weight, the presence of mucositis at baseline, serum glutamic pyruvid transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), total bilirubin (BIL), gamma-

glutamyl transferase (GGT), presence of Neutropenia at baseline (NEU), occurrence of diarrhea (DIA), and the occurrence of vomiting (VOM). The effects of these covariates on the pharmacokinetic parameters of POS were investigated. In addition, the effect of intake of proton pump inhibitors (PPI) and H2 antagonists (H2A) on the PK of POS was investigated. Finally, the relationship between PK parameter estimates and the occurrence of IFIPP (Invasive Fungal Infection Proven or Probable) or IFIPPP (Invasive Fungal Infection Proved, Probable, or Possible) was investigated in a similar manner as categorical covariates. The bioavailability of POS has been shown to be significantly lower in fasting healthy volunteers relative to that in the fed state. However, no food intake data was available in this study and the effect of food on the plasma exposures of POS was not investigated.

Categorical covariates were investigated using the power model. For example, the effect of Race on V/F (V in NonMem) was incorporated into the model using the following equation:

$$V_i = TVV * Theta^{**RACE*} exp(eta)$$

where Vi is the individual predicted volume of distribution, TVV is the typical value of V (population mean value), and eta is a normally distributed value with a mean of zero (exponential or log-normal distribution of inter-subject variability in V). RACE is equal to 1 when individual is Caucasian and zero when the patient in non-Caucasian. As a result, the estimate of Theta represents the relationship between the mean estimates of Vi for Caucasians versus non-Caucasians.

Continuous covariates were introduced using the power model after correcting them with the mean value of that covariate. For example, the effect of age on the estimate of Vi was investigated using the following equation:

$$V_i = TVV * (Age/48.5)^{**Theta*} exp(eta)$$

where Vi is the individual predicted volume of distribution, TVV is the typical valued of V (population mean value), and eta is the a normally distributed value with a mean of zero (exponential or log-normal distribution of inter-subject variability in V), Age is the age for that patient, and 48.5 is the mean value of Age for the POS group (with PK data).

Covariates were investigated using a two-stage approach. First, a "Stepwise Forward Addition" was used and covariates with a change in the Objective function of $\geq$3.84 were incorporated one at a time. A second stage involved adding all the "significant" covariates from the first Stage (i.e., Stepwise Forward Addition) in one model (called Full Model) and then performing "Stepwise Backward Elimination". Covariates that, when eliminated, caused a change greater than 10.88 in the Objective Function Value (OBJF) were kept in the model. The choice of the significant OBJF value was set a priori.

Covariates were assumed to affect V/F (apparent volume of distribution estimate, expressed as V in NonMem). Due to the nature of the data available, the model couldn't distinguish between the effect on V (true volume of distribution) and the effect on F

(bioavailability estimate). In other words, higher estimated V/F could mean higher volume of distribution estimate or a lower bioavailability estimate. Both will lead to lower exposures observed.

Since most of the data available in this study was at steady state conditions with no terminal phase defined, the typical value (population mean value) of half life was fixed at 35h [k □0.0198 $h^{-1}$]. Inter-subject variability of the k value was allowed assuming exponential (log-normal) distribution around the mean.
Inter-subject variability around the mean value of ka and V was also assumed to have log-normal distribution. The same value of eta was assumed for both V and ka since the value of V in NonMem is actually V/F and the value of ka is actually ka*F, the same eta was used for both V and V/F.

Intra-subject (inter-occasion) variability was allowed and investigated with additive, proportional, and exponential models. An exponential model was then chosen based on the diagnostic plots. Model evaluation was performed using the OBJF value and diagnostics plots of Predicted versus Observed, Individual Predicted (ipred) Versus Observed, Residual, Weighted Residuals, and Predicted/Observed versus time plots.

The First Order Conditional Estimation method (FOCE, Method = 1 in NonMem) was used in the final model and covariate analysis. Initial parameter estimates for the FOCE method were used from successful NonMem runs with the First Order method (FO, Method = 0 in NonMem). Since plasma sampling in this study was sparse, $T_{max}$ estimation from observed data was deemed inappropriate. Additionally, data from all patients was analyzed simultaneously using NonMem regardless whether patients had extensive plasma sampling. Finally, in this clinical study, the number of breakthrough IFI infections was very low as a result of successful prophylaxis. Therefore a proper evaluation of the relationship between exposure response and AUC/MIC could not be conducted.

***Software***

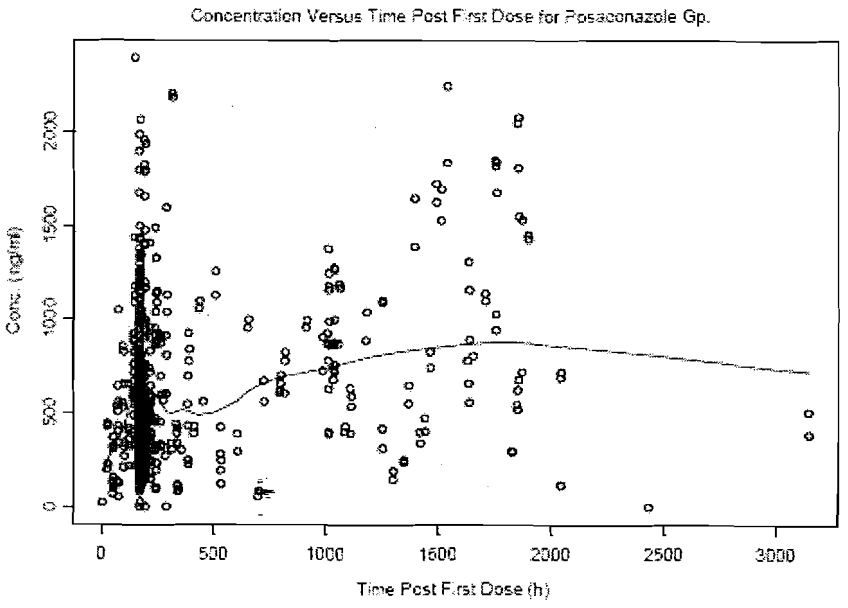
The software used for the data formatting was Splus and for performing the population PK analysis, NONMEM was used.

## Results and Discussion

***Data Integrity***

All patients are included in the NonMem data sets Only 3 concentration time points were excluded as listed below:
a. Patient 001125 at 195hr and 289hr time points only.
b. Patient 001018 at 2431.33hr time point only.

The concentration-time profile for all subjects receiving posaconazole oral suspension 200 mg TID is given below:




***Model and Model Selection:***

**Final Model**

**Model description**

Seven covariates were included in the "Full Model" following the Stepwise Forward Addition stage: DIA (Diarrhea), PPI (Intake of Proton Pump Inhibitors), IFIPP (Reported Invasive Fungal Infection, Proved or Probable), BIL (billirubin higher than twice the upper limit of normal), Baseline Body Weight, GGT liver enzymes higher than twice the upper limit of normal, and Race (Caucasian versus Non-Caucasian).

The Stepwise Backward Elimination Stage identified Baseline Body Weight and IFIPP as insignificant variables. The final model included five covariates as significant: DIA, PPI, BIL, GGT, and RACE (Caucasian versus Non-Caucasian).
The final estimated effects of the significant covariates on V/F estimate are included in Table 1. The model run numbers and comparisons of the OBJF values from each run of the Backward Elimination Stage are presented in Table 2.

**Table 1** Summary of Magnitude of Predicted Effects of Significant Covariates on V/F

| Covariate | Estimated Effect on V/F (± Std. Error) | Estimated Effect on Exposure (Equals 1/Estimated Effect on V/F) |
|---|---|---|
| DIA | 1.5 ± 0.20 | 0.667 |
| PPI | 1.43 ± 0.17 | 0.699 |
| BIL | 1.84 ± 0.33 | 0.544 |
| GGT | 1.17 ± 0.095 | 0.855 |
| RACE (Caucasian vs. Non-Caucasian) | 0.79 ± 0.065 | 1.266 |

Table 2. Model runs in the stepwise backward elimination stage

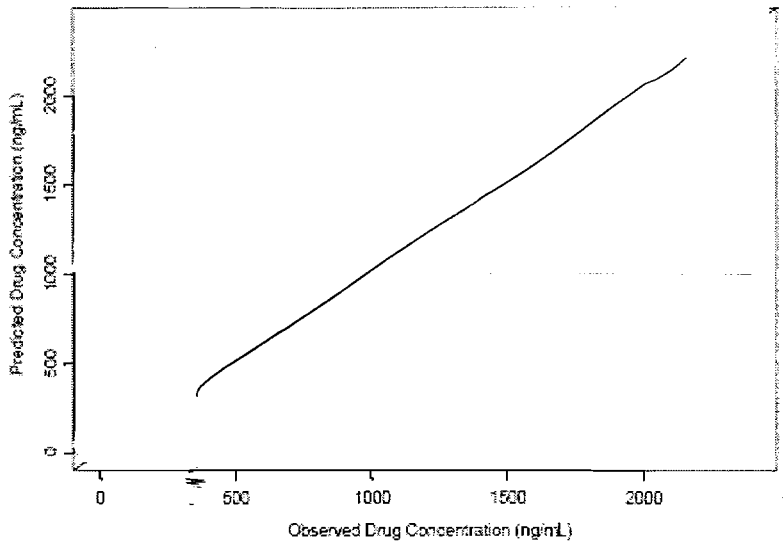
**Model Runs in the Stepwise Backward Elimination Stage**

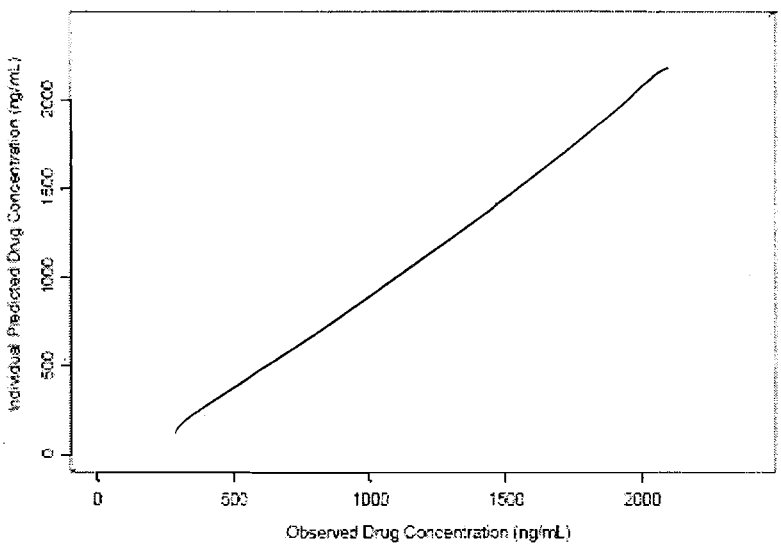
| Run # | Covariates | OBJF | Parameter | Value | Comments | OBJF Comparison |
|---|---|---|---|---|---|---|
| 131 | DIA&PPI&IFIPP&GGT&BIL&WT&RACE | 8350 | ke | 0.0198 | Fixed ke to .0198. Eta(2) Related to ka and V. | BACKWARD ELIMINATION BASELINE |
| | ALL FACTORS WITH SIGNIFICANCE OF OBJ FUNC OF >3.5 WERE ADDED IN ONE AS A BASE FOR BACKWARD STEPWISE ELIMINATION | | V | 3380 | | |
| | | | ka | 0.0428 | | |
| | | | Om1 CV% | 50 | | |
| | | | Om2 CV% | 39.1 | | |
| | | | EPS CV% | 31.4 | | |
| | | | THETA4 | 1.6 | DIA ON V/F | |
| | | | THETA5 | 1.39 | PPI ON V/F | |
| | | | THETA6 | 1.21 | IFIPP ON V/F | |
| | | | THETA7 | 1.66 | BILL ON V/F | |
| | | | THETA8 | 0.39 | WT (POWER) ON V/F | |
| | | | THETA9 | 1.2 | GGT ON V/F | |
| | | | THETA10 | 0.783 | CAUCASIAN ON V/F | |
| 132 | DIA&PPI&IFIPP&GGT&BIL&WT&RACE | 8425 | ke | | Fixed k to .0198. Eta(2) Related to ka and V. | 75 |
| | THETA 4 (DIA) WAS FIXED TO 1. Looking for an increase in OBJF by more than 10.86 to keep the effect. DIA IS SIGNIFICANT AND WILL BE KEPT. | | V | | | |
| | | | ka | | | |
| | | | Om1 CV% | | | |
| | | | Om2 CV% | | | |
| | | | EPS CV% | | | |
| | | | THETA4 | FIXED | DIA ON V/F | |
| | | | THETA5 | | PPI ON V/F | |
| | | | THETA6 | | IFIPP ON V/F | |
| | | | THETA7 | | BILL ON V/F | |
| | | | THETA8 | | WT (POWER) ON V/F | |
| | | | THETA9 | | GGT ON V/F | |
| | | | THETA10 | | CAUCASIAN ON V/F | |
| 133 | DIA&PPI&PP&GGT&BIL&WT&RACE | 8360.4 | ke | | Fixed k to .0198. Eta(2) Related to ka and V. | 30.4 |
| | THETA 5 (PPI) WAS FIXED TO 1. Looking for an increase in OBJF by more than 10.86 to keep the effect. Compared to run 130, PPI IS SIGNIFICANT AND WILL BE KEPT. | | V | | | |
| | | | ka | | | |
| | | | Om1 CV% | | | |
| | | | Om2 CV% | | | |
| | | | EPS CV% | | | |
| | | | THETA4 | | DIA ON V/F | |
| | | | THETA5 | FIXED | PPI ON V/F | |
| | | | THETA6 | | IFIPP ON V/F | |
| | | | THETA7 | | BILL ON V/F | |
| | | | THETA8 | | WT (POWER) ON V/F | |
| | | | THETA9 | | GGT ON V/F | |
| | | | THETA10 | | CAUCASIAN ON V/F | |
| 134 | DIA&PPI&PP&GGT&BIL&WT&RACE | 8351.2 | ke | | Fixed k to .0198. Eta(2) Related to ka and V. | 1.2 |
| | THETA 6 (PP) WAS FIXED TO 1. Looking for an increase in OBJF by more than 10.86 to keep the effect. Compared to run 131, IFIPP IS INSIGNIFICANT AND WILL NOT BE KEPT. | | V | | | |
| | | | ka | | | |
| | | | Om1 CV% | | | |
| | | | Om2 CV% | | | |
| | | | EPS CV% | | | |
| | | | THETA4 | | DIA ON V/F | |
| | | | THETA5 | | PPI ON V/F | |
| | | | THETA6 | FIXED | IFIPP ON V/F | |
| | | | THETA7 | | BILL ON V/F | |
| | | | THETA8 | | WT (POWER) ON V/F | |
| | | | THETA9 | | GGT ON V/F | |
| | | | THETA10 | | CAUCASIAN ON V/F | |

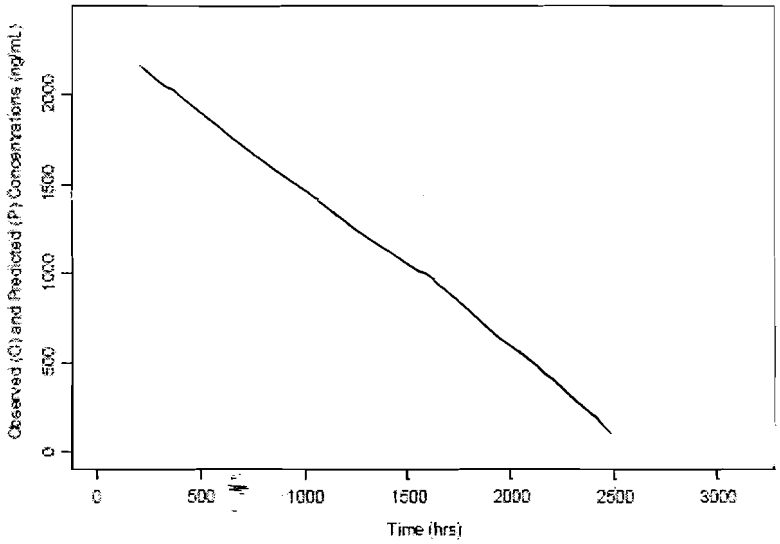
| Run # | Covariates | OBJF | Parameter | Value | Comments | OBJF Comparison |
|---|---|---|---|---|---|---|
| 135 | D:A&PPI&GGT&BIL&WT&RACE | 8351.2 | ke | 0.0198 | | New BASE |
| | THIS IS A RUN WITHOUT IFIPP. IT WILL SERVE AS BASE FOR NEXT RUNS. | | V | 3420 | | |
| | | | ka | 0.0431 | Fixed k to .0198. Eta(2) Related to ka and V. | |
| | | | Om1 CV% | 49.1 | | |
| | | | Om2 CV% | 39.1 | | |
| | | | EPS CV% | 31.4 | | |
| | | | THETA4 | 1.5 | DIA ON V/F | |
| | | | THETA5 | 1.38 | PPI ON V/F | |
| | | | THETA6 | 1.71 | BILL ON V/F | |
| | | | THETA7 | 0.395 | WT (POWER) ON V/F | |
| | | | THETA8 | 1.19 | GGT ON V/F | |
| | | | THETA9 | 0.782 | CAUCASIAN ON V/F | |
| 136 | D:A&PPI&GGT&BIL&WT&RACE | 8401.9 | ke | 0.0198 | | 50.7 |
| | THIS IS A RUN WITHOUT RACE. LOOKING FOR AN INCREASE IN OBJF BY MORE THAN 10.88 TO KEEP RACE IN THE EQUATION. race will be kept. Compared to Run 135 | | V | 1750 | | |
| | | | ka | 1.1600 | Fixed k to .0198. Eta(2) Related to ka and V. | |
| | | | Om1 CV% | 56.2 | | |
| | | | Om2 CV% | 38.6 | | |
| | | | EPS CV% | 35.1 | | |
| | | | THETA4 | 1.53 | DIA ON V/F | |
| | | | THETA5 | 1.47 | PPI ON V/F | |
| | | | THETA6 | 1.67 | BILL ON V/F | |
| | | | THETA7 | 0.391 | WT (POWER) ON V/F | |
| | | | THETA8 | 1.15 | GGT ON V/F | |
| | | | THETA9 | FIXED | CAUCASIAN ON V/F | |
| 137 | D:A&PPI&GGT&BIL&WT&RACE | 8364.9 | ke | 0.0198 | | 13.7 |
| | THIS IS A RUN WITHOUT GGT. LOOKING FOR AN INCREASE IN OBJF BY MORE THAN 10.88 TO KEEP GGT IN THE EQUATION. Compared to Run 135. GGT is significant and will not be removed. | | V | | | |
| | | | ka | | Fixed k to .0198. Eta(2) Related to ka and V. | |
| | | | Om1 CV% | | | |
| | | | Om2 CV% | | | |
| | | | EPS CV% | | | |
| | | | THETA4 | | DIA ON V/F | |
| | | | THETA5 | | PPI ON V/F | |
| | | | THETA6 | | BILL ON V/F | |
| | | | THETA7 | | WT (POWER) ON V/F | |
| | | | THETA8 | FIXED | GGT ON V/F | |
| | | | THETA9 | | CAUCASIAN ON V/F | |
| 138 | D:A&PPI&GGT&BIL&WT&RACE | 8367.5 | ke | 0.0198 | | 16.3 |
| | THIS IS A RUN WITHOUT BIL. LOOKING FOR AN INCREASE IN OBJF BY MORE THAN 10.88 TO KEEP BIL IN THE EQUATION. Compared to Run 135. BIL is significant and will not be removed. | | V | | | |
| | | | ka | | Fixed k to .0198. Eta(2) Related to ka and V. | |
| | | | Om1 CV% | | | |
| | | | Om2 CV% | | | |
| | | | EPS CV% | | | |
| | | | THETA4 | | DIA ON V/F | |
| | | | THETA5 | | PPI ON V/F | |
| | | | THETA6 | FIXED | BILL ON V/F | |
| | | | THETA7 | | WT (POWER) ON V/F | |
| | | | THETA8 | | GGT ON V/F | |
| | | | THETA9 | | CAUCASIAN ON V/F | |
| 139 | D:A&PPI&GGT&BIL&WT&RACE | 8360 | ke | 0.0198 | | 8.8 |
| | THIS IS A RUN WITHOUT WT. LOOKING FOR AN INCREASE IN OBJF BY MORE THAN 10.88 TO KEEP WT IN THE EQUATION. WT SHOULD NOT BE INCLUDED IN THIS MODEL. Run is compared to Run 135. THIS MODEL RUN (139) IS THE FINAL MODEL WITH COVARIATES | | V | 3290 | | |
| | | | ka | 0.0398 | Fixed k to .0198. Eta(2) Related to ka and V. | |
| | | | Om1 CV% | 47 | | |
| | | | Om2 CV% | 39.5 | | |
| | | | EPS CV% | 32.1 | | |
| | | | THETA4 | 1.50 | DIA ON V/F | |
| | | | THETA5 | 1.43 | PPI ON V/F | |
| | | | THETA6 | 1.84 | BILL ON V/F | |
| | | | THETA7 | FIXED | WT (POWER) ON V/F | |
| | | | THETA8 | 1.17 | GGT ON V/F | |
| | | | THETA9 | 0.787 | CAUCASIAN ON V/F | |

**Goodness of fit**

The diagnostic plots for the final model are given below:

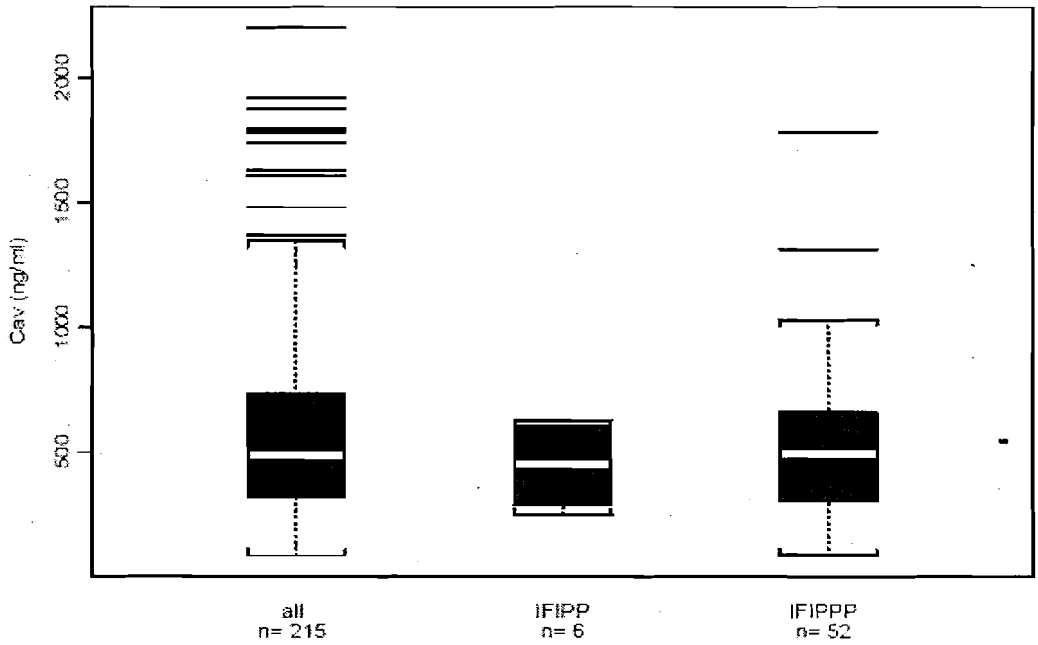





**Effect of Covariates on Average Concentrations**

Subjects with IFIPP and IFIPPP have Cav values that are not different from the entire sampled population. This is demonstrated below.

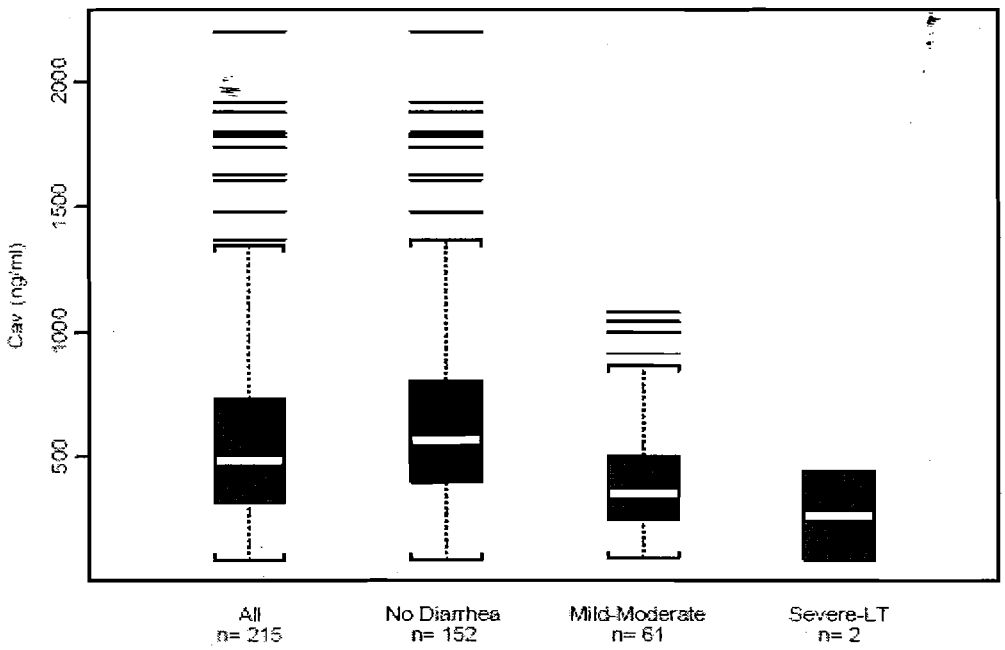



No association was found between $C_{av}$ and gender (P=0.2654), baseline mucositis (P=0.1002), the presence of neutropenia (P=0.7588), occurrence of vomiting (P=0.6842), or H2-receptor antagonist intake (P=0.9129).

Subjects with elevated GGT higher than twice the upper limit of normal (GGT $\geq$2 x ULN) had $C_{av}$ values that were lower than those with GGT <2 x ULN

(P=0.0093). The difference between the mean $C_{av}$ of these two groups is less than 30% and is not considered clinically relevant. A possible explanation for a lower $C_{av}$ value in subjects with GGT ≥2 x ULN could be that the subjects secreted comparatively less bile salts which are postulated to help solubilize POS in the GI tract. When all liver enzymes are taken into consideration, there was no difference in mean $C_{av}$ values between subjects with any liver enzymes ≥2 x ULN and subjects with liver enzymes <2 x ULN (P=0.8196).

As expected for most orally administered drugs, $C_{av}$ in subjects with recorded diarrhea was lower (P<0.0001) than those with no recorded diarrhea. The effect of diarrhea on $C_{av}$ appeared to increase with its severity.




Caucasians had, on average, higher $C_{av}$ values compared to non- Caucasians (P=0.0132).

Finally, subjects who received PPIs in the POS group had $C_{av}$ values that were lower than subjects who had not received PPIs (P<0.0001). The ratio of $C_{av}$ values (PPIs/no PPIs) was 0.71 (90% CI, 0.62-0.81).

In summary, $C_{av}$ was found to be affected by four factors: diarrhea, GGT ≥2 x ULN, race and PPI intake. The table of subjects with IFIPP shows that none of these factors had a prevailing occurrence in these subjects is given below. Out of the 7 subjects with IFIPP, only 2 received a PPI, no subject had GGT ≥2 x ULN, and only 2 subjects had mild to moderate diarrhea. Five out of the 7 subjects with IFIPP were Caucasian. This leads to the conclusion that despite statistically significant differences in $C_{av}$ values due to diarrhea, PPI intake, GGT ≥2 x ULN, and race, adequate plasma levels were attained in subjects for successful prophylaxis against IFIs.

| Site No. | Subj. No. | Gender | Race | GGT | LIV | Diarrhea | PPINHIB |
|---|---|---|---|---|---|---|---|
| 2 | 1271 | M | Caucasian | 0 | 0 | 0 | 0 |
| 10 | 1371 | F | Asian | 0 | 0 | 0 | 0 |
| 15 | 1239 | M | Caucasian | 0 | 1 | 1 | 0 |
| 15 | 1415 | F | Caucasian | 0 | 0 | 0 | 0 |
| 54 | 1468 | F | Hispanic | 0 | 0 | 1 | 0 |
| 57 | 1492 | M | Caucasian | 0 | 1 | 0 | 1 |
| 41 | 1329 | F | Caucasian | 0 | 0 | 0 | 1 |

no = 0, yes = 1.

F = female; GGT = gamma-glutamyl transpeptidase; IFI = invasive fungal infection; LIV = hepatic laboratory test; M = male; PPINHIB = proton pump inhibitor; Site No. = site number; Subj. No. = subject number.

## Reviewer's Comments

- The method and interpretation of population PK analyses to see the effect of covariates, e.g., patients demographic, on posaconazole PK seem appropriate from the perspective of Clinical Pharmacology and Biopharmaceutics.

- The sponsor has not performed the post hoc step in NONMEM to obtain estimates of the PK parameters such as AUC, CL, Vd etc.

## Recommendations

*Labeling*

1. Please add a table to the clinical pharmacology section of the label to include the PK parameters such as steady state average concentrations, oral clearance, volume of distribution, AUC and elimination half-life of posaconazole.

### 4.2.1. POS PK in pediatric patients

In Studies P01899 and C98316, $C_{avg}$ were available in 10 adolescents (13-17 years of age). The descriptive statistics of $C_{avg}$ in adolescents are summarized in Table 1. Since these values were similar to patients ≥ 18 years of age. Thus, it appears appropriate to use the same dosing regimen for patients 13-17 years of age as adults (≥ 18 years of age).

**Table 1.** Steady-state average POS concentration in patients 13-17 years of age and adults (≥ 18 years of age) (Studies C98316 and P01899)

| | N | Mean±SD | Median [Range] |
|---|---|---|---|
| 13-17 years of age | 10 | 760±404 | 682 [254-1370] |

## 4.3 OCP 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** | **22-003** | **Brand Name** | **Noxafil** |
| **OCP Division** | **DCP IV** | **Generic Name** | **Posaconazole** |
| **Medical Division** | **DSPTP** | **Drug Class** | **Triazoel Antifungal** |
| **OCP Reviewer** | **Seong H. Jang** | **Indication(s)** | **Prophylaxis of invasive fungal infections** |
| **OCP Team Leader** | **Philip Colangelo** | **Dosage Form** | **Oral suspension (40 mg/mL)** |
| | | **Dosing Regimen** | **200 mg TID** |
| **Date of Submission** | **12/22/05** | **Route of Administration** | **Oral** |
| **Estimated Due Date of OCPB Review** | **05/22/05** | **Sponsor** | **Schering-Plough Corp** |
| **PDUFA Due Date** | **06/22/06** | **Priority Classification** | **Priority (6 months)** |
| **Division Due Date** | | | |
| **Advisory committee metting** | **N/A** | | |

### *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:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| **Healthy Volunteers-** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Patients- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |

| | | | | |
|---|---|---|---|---|
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | X | 2 | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | | | | |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **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 | **Comments** |
|---|---|---|
| **Application filable ?** | X | Reasons if the application is not filable (or an attachment if applicable)<br>For example, is clinical formulation the same as the to-be-marketed one? |
| **Comments sent to firm ?** | | Comments have been sent to firm (or attachment included). FDA letter date if applicable. |
| **QBR questions (key issues to be considered)** | | |
| **Other comments or information not included above** | | |
| **Primary reviewer Signature and Date** | | |
| **Secondary reviewer Signature and Date** | | |

CC: NDA 22-003

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

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/s/

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Seong Jang
6/20/2006 04:12:08 PM
BIOPHARMACEUTICS

Phil Colangelo
6/20/2006 04:40:06 PM
BIOPHARMACEUTICS