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| **Official Protocol Title:** | Pharmacokinetics and Safety of Intravenous Posaconazole (MK-5592, POS) in Chinese Subjects at High Risk for Invasive Fungal Infections |
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**TITLE:**

Pharmacokinetics and Safety of Intravenous Posaconazole (MK-5592, POS) in Chinese Subjects at High Risk for Invasive Fungal Infections

**IND NUMBER:** Not Applicable
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## 1.0 TRIAL SUMMARY

| | |
|---|---|
| Abbreviated Title | Pharmacokinetics and Safety of Intravenous Posaconazole (MK-5592, POS) in Chinese Subjects at High Risk for Invasive Fungal Infections |
| Trial Phase | Phase I b |
| Clinical Indication | Prophylaxis of invasive fungal infections |
| Trial Type | Interventional |
| Type of control | No treatment control |
| Route of administration | Intravenous |
| Trial Blinding | Unblinded Open-label |
| Treatment Groups | Only one treatment regimen |
| Number of trial subjects | Approximately 70 subjects will be enrolled. |
| Estimated duration of trial | The sponsor estimates that the trial will require approximately 10 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit. |
| Duration of Participation | Each subject will participate in the trial for approximately 84 days from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of 14 days, each subject will be receiving POS intravenous (IV) solution 300 mg Q12h on Day 1, followed by 300 mg QD on Day 2 through 10 (±1) via central line administration. Then, subjects will receive IV solution 300 mg QD or oral suspension 200 mg TID for up to 18 (±1) days at the discretion of investigator. The total treatment duration is at least 10 (±1) days to up to 28 days. After the end of treatment (EOT) each subject will be followed for 30 days for safety. Also, subjects will have a survival assessment at any day from Days 60 to 70. |

A list of abbreviations used in this document can be found in Section 12.11.

## 2.0 TRIAL DESIGN

### 2.1 Trial Design

This is an open-label, single arm, multi-center, and two sub-groups trial of MK-5592 in Chinese Subjects at High Risk for Invasive Fungal Infections (IFIs) to be conducted in conformance with Good Clinical Practices.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

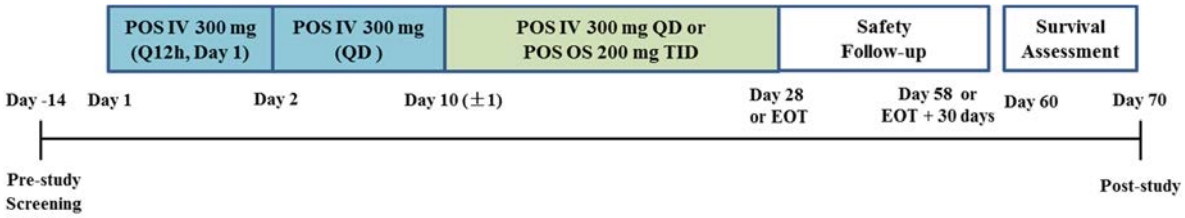
## 2.2 Trial Diagram

This is an open-label, single arm, multi-center study with two sub-groups. At least 3 investigative sites in China will be selected for this study.

Subjects will be allocated to one treatment group with same treatment regimen; while there will be 2 subgroups for different pharmacokinetic sampling schemes as indicated below (Figure 1, Trial Design). Approximately 30 subjects will be allocated to subgroup 1, and about 40 subjects will be allocated to subgroup 2. The two subgroups will receive same treatment but different blood sample collection schemes in order to characterize the pharmacokinetics in the whole study population.

After a screening phase of 14 days, each subject will receive POS intravenous (IV) solution 300 mg Q12h on Day 1, followed by 300 mg QD on Day 2 through 10 (±1) via central line administration. Then, subjects will receive IV solution 300 mg QD or oral suspension (OS) 200 mg TID for up to 18 (±1) days at the discretion of investigator. The investigator could switch the subject back to POS IV solution treatment during oral treatment period if the subject is unable to tolerate oral suspension. The total treatment duration is at least 10 (±1) days to up to 28 days. After the end of treatment (EOT), each subject will be followed for 30 days for safety. A survival assessment will be performed on any day from Days 60 to 70.

The trial design is depicted in Figure 1.




- For subgroup 1, blood samples for plasma trough POS levels will be drawn on Days 3, 6, 10 (± 1), 15 (± 1), 22 (± 1), and 28/EOT. Additional PK samples will be drawn on Day 10 (± 1) at pre-dose, 1 hour post start of infusion, immediately before the end of infusion, approximately 15 minutes after the end of infusion, and approximate 4, 8, 12 and 24 hours post start of infusion. The intensive PK for POS IV solution on Day 10 (± 1) must be obtained before switching to oral suspension.
- For subgroup 2, blood samples for plasma trough POS levels will be drawn on Days 3, 6, 10 (± 1), 15 (± 1), 22 (± 1), and 28/EOT.

Figure 1 Study Design

# 3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

## 3.1 Primary Objective(s) & Hypothesis(es)

**Objective:** To characterize the pharmacokinetics of POS IV solution in Chinese subjects at high risk for invasive fungal infections.

**Hypothesis:** The pharmacokinetics parameters (e.g., steady-state $C_{avg}$, $AUC_{0\text{-}24hr}$) of POS IV solution in Chinese subjects at high risk of invasive fungal infections will be estimated. Percentage of Chinese subjects with steady-state $C_{avg} \geq 500$ ng/ml will be estimated.

## 3.2 Secondary Objective(s) & Hypothesis(es)

**Objective**: To evaluate the safety and tolerability of POS IV solution in Chinese subjects at high risk for invasive fungal infection.

# 4.0 BACKGROUND & RATIONALE

## 4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-5592.

### 4.1.1 Pharmaceutical and Therapeutic Background

Invasive fungal infections (IFIs) are an important cause of morbidity and mortality in patients receiving treatment for hematologic disease. In particular, patients with prolonged neutropenia and/or severe immunosuppression are at increased risk.

MK-5592, or Posaconazole (POS), a broad-spectrum triazole antifungal compound discovered by Merck Research Laboratories, exhibits potent antifungal activity against a variety of yeasts and molds, including strains that are resistant to amphotericin B (AMB), fluconazole (FLZ), voriconazole (VOR), or itraconazole (ITZ). The mechanism of action, selective inhibition of the α-C14 demethylase (a member of CYP P450 cytochrome system; CYP51A) involved in ergosterol biosynthesis of yeast and filamentous fungi, is similar to that of the other azoles. Therefore, POS has an important role in the prophylaxis and treatment of IFIs against *Aspergillus*, *Candida*, *Zygomycete*s and *Fusarium* infections [1].

POS IV solution was approved (Noxafil IV) for prophylaxis of patients with high risk of IFIs by FDA in Mar-2014, and also approved by EMA in Sep-2014.

In EU and US, the POS IV solution was approved by bridging with oral suspension. A Phase 1B/3 study (Study P05520) [2] was conducted as a PK and safety bridging study and sought to bridge to exposures within the pre-defined target exposure range previously found to be safe and efficacious based on trials of POS oral suspension. Based on the exposure-response relationship found in earlier controlled studies of POS oral suspension in the prophylaxis of IFI setting (C/I98 -316 and P01899) as well as the studies that were conducted in the refractory IFI setting (P00041), with higher exposures associated with a higher likelihood of clinical response, clinical response was greater with increasing exposure to POS, with responses of >70% in the highest quartile (4th quartile) of exposure. By contrast, no association was demonstrated with high concentrations of POS and adverse experiences in the previous POS oral suspension controlled studies. The ranges of desirable exposure agreed with FDA/EMA as shown below:

- Mean steady-state $C_{avg}$ of approximately 1,200 ng/mL, with at least 90% of the subjects between 500 ng/mL and 2,500 ng/mL.
- No subject with $C_{avg}$ at steady-state above 3,650 ng/mL.
- No subject with $C_{avg}$ at steady-state below 200 ng/mL.

To support the bridging concept, a population PK model was developed including the data from the 3 healthy volunteer studies (P04985, P06356 and P07783) and 1 study in high-risk subjects (P05520) for simulation purposes and calculation of the relevant exposure parameters ($AUC_{\tau}$, $C_{avg}$, and $C_{min}$). Simulations with the population PK model indicated that after once-daily maintenance administration of 300 mg POS IV solution (following Q12h dosing on Day 1), 99.7% and 93.6% of the high-risk subjects have a $C_{avg}$ and $C_{min}$ above 500

ng/mL, respectively, thereby achieving exposures that are known to be effective and well tolerated as prophylaxis against IFIs.

Based on previous knowledge of pharmacokinetic profile and its metabolism pathway, there is no apparent ethnic difference in pharmacokinetics of POS. Similar bridging strategies will be used in this project.

POS was developed initially as an oral suspension. The oral POS suspension (Noxafil®) is a white, opaque, immediate release, formulation with a concentration of 40 mg/mL, which was launched in China in June 2013. It is known that the absorption of POS after oral administration is relatively low and less predictable, especially in patients who are fasting or who have limited oral intake due to gastrointestinal diseases such as diarrhea or chemotherapy-induced mucositis. The exposure of POS oral suspension is influenced by food, and high fat food could increase the exposure of oral suspension. Exposure to posaconazole oral suspension after a single dose was increased by about 2.6-fold when given with a nutrient supplement and by about 4-fold when given with a high-fat meal.

Since the efficacy of POS could be limited by the extent of exposures and sick patients are not reliably taking sufficient food to boost the exposure of POS, new IV formulations of POS have been developed to achieve a higher, more predictable exposure with reduced variability compared to POS oral suspension. POS IV solution is an aqueous injectable solution containing 18 mg/mL of POS to be diluted in 5 % dextrose in water or sodium chloride 0.9% prior to IV administration. The primary excipient in POS IV Solution is sulfobutylether-β-cyclodextrin (SBEβCD). The new IV formulations are administered as once daily (QD). Phase Ib studies have been conducted in Caucasian patients treated with POS IV solution given as antifungal prophylaxis. In Caucasian patients, the mean steady-state $C_{avg}$ exposure for POS IV solution 300 mg QD was 1500 ng/ml. With this new formulation, the desired exposure target (steady-state $C_{avg}$ around 1200 ng/mL) was more consistently achieved. This target concentration is associated with a higher response rate in subjects with invasive aspergillosis [2].

Besides posaconzole, IV formulation of other antifungal agent (such as itraconazole) has also been developed to show the benefits of IV formulation in the prophylaxis of IFIs. The PK studies of itraconazole show that the bioavailability of IV formulation is better than capsule and oral solution, and could achieve the desired steady plasm drug concentration more quickly [3]. Clinical studies of itraconazole show that the IV formulation could use for the treatment and prophylaxis of IFI [4, 5] and could be used as sequential therapy. Traditionally, the treatment or prophylaxis of bacterial infections and IFI is initially with intravenous therapy, followed by physician-directed switch to oral therapy. Also, the cost-effectiveness of sequential therapy is better than oral therapy alone. Therefore, the sequential therapy of antifungal agent has been used widely in clinics. In China, some studies show that the prophylactic effect of sequential therapy of itraconazole for Prophylaxis of IFI is better than systemic antifungal therapy alone, and the adverse events did not increase [6].

## 4.2 Rationale

### 4.2.1 Rationale for the Trial and Selected Subject Population

To support China registration of IV solution, PK in Chinese needs to be characterized. Similar with global registration strategies, China registration strategy will also use a population PK study to establish the exposure in Chinese and bridge with previously established exposures of POS oral suspension as basis for approval. The subjects in this population PK study will be the subjects with high risk of IFIs due to being severely immunocompromised, such as those with hematologic malignancies with prolonged neutropenia from chemotherapy. This population are the future targeted population, and also are similar with the subjects in global IV pivotal study (i.e. P05520). In China, a healthy volunteer PK study for oral suspension was conducted already, and the results are comparable with that in global studies. To support China registration of IV solution, a healthy volunteer PK (PN111) was finished, and a population PK study (PN120, i.e. this protocol) in prophylaxis population will be conducted.

In China, POS oral suspension has been approved for prophylaxis of invasive fungal infection. The patients at risk for invasive fungal infection include neutropenia. Neutropenic Chinese subjects between 18 to 70 (inclusive) years of age undergoing chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) with high risk of IFIs will be enrolled in this study. This study population is consistent with the approved indication for the oral suspension.

Details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

In this study, patients at risk for invasive fungal infection will be enrolled.

### 4.2.2 Rationale for Dose Selection/Regimen

The objective of this study is to characterize the PK and safety profiles of POS IV Solution in Chinese subjects at high risk for invasive fungal infection. Global Phase Ib/III studies have been conducted in patients (AML/MDS and HSCT) treated with POS IV solution given as antifungal prophylaxis. In the global phase 1b/III study, the two doses of POS have been investigated. The 300 mg dose was selected as the final clinical dose. Among 49 serial PK-evaluable subjects treated with 300 mg dose of POS IV solution, 46 of 49 (94%) subjects attained steady-state $C_{avg}$ between 500 ng/mL and 2500 ng/mL and 3 of 49 (6%) subjects attained steady-state $C_{avg}$ between 2500 ng/mL and 3650 ng/mL. None of these 49 subject's steady-state $C_{avg}$ was below 500 ng/mL or exceeded 3650 ng/mL. These exposure data are within desirable ranges to be efficacious and safe. The safety of the drug when given to all subjects was closely evaluated. POS IV solution at a dose of 300 mg QD (following 300 mg Q12h loading dose at Day 1) was well tolerated in this patient population and the safety profile seen in the study was similar to that previously reported for POS oral suspension [7].

The approved dose by FDA and EMA is 300 mg Q12h for the first day, and then 300 mg QD for the rest of the treatment therapy. This dosing regimen was evaluated in a Phase 1b/3 study (P05520) designed to demonstrate that this dosing regimen could provide POS exposure within the pre-defined target exposure range as indicated above. Based on previous knowledge of pharmacokinetic profile and its metabolism pathway, there is no apparent

ethnic difference in pharmacokinetics of POS IV expected. So the same dose and dose regimen as that approved in US and Europe has been selected for this study. Also based on the physician's judgment, the patients could also be switched to oral suspension or oral tablet. In China, only oral suspension formulation was approved, so in this study, the patients could be switched to oral suspension only.

#### 4.2.2.1 Starting Dose for This Trial

Posaconazole has a half-life of approximately 30 hours. It may take 6-8 days to reach steady-state. It is desirable to achieve therapeutic level promptly, so a loading dose of two times 300 mg treatment on first day has been used for this study.

#### 4.2.2.2 Maximum Dose/Exposure for This Trial

The duration for this study is related to the duration at risk for invasive fungal infection. Twenty-eight days' treatment duration was considered to be adequate to address the study objective and provide potential medical benefits for study subjects.

#### 4.2.2.3 Rationale for Dose Interval and Trial Design

The pharmacokinetic profile of posaconazole supports its once daily dose interval and once daily dosing is also very desirable for better compliance.

There is no restriction on food intake for POS IV solution treatment. In this study, the follow up treatment could be oral suspension of POS, which was approved for prophylaxis of IFIs in China. For POS oral suspension administration, drug should be given under the guidance of physicians and local label and should be administered with food or immediately after eating (i.e., within 20 minutes). Based on prior study experiences, to achieve high exposure of POS oral suspension, high fat food would be recommended with dosing if the subjects could tolerate. The food intake information during oral suspension dosing period will be recorded in the study medication diary.

Considering the objective nature of study, an open label study is considered to be adequate to serve its purpose.

### 4.2.3 Rationale for Endpoints

#### 4.2.3.1 Pharmacokinetic Endpoints

In this study, primary key parameter: Steady-state of $C_{avg}$, where $C_{avg}$ is defined as $AUC_{0\text{-}24hr}$ divided by the dosing interval.

Other parameters: $C_{min}$, $C_{max}$, $T_{max}$, $AUC_{0\text{-}24hr}$ determined from plasma samples taken at steady-state as described under Study Procedures. In addition, the POS plasma concentration-time data were to be used to estimate the following PK parameters, as the data allowed:

- $C_{min}$ – POS trough level immediately before a subject receives the dose of POS IV solution on the day specified in the protocol.
- $C_{max}$ – Observed maximum plasma concentration.
- $T_{max}$ – Time of observed maximum plasma concentration.

- AUC – Area under the plasma concentration versus time curve.
- CL – Total body clearance.

Besides $C_{min}$ which could be observed from subgroup 2, all other observed parameters are from subgroup 1, and the rest parameters are calculated.

The time points for PK samples as below for each sub-group.

Subgroup 1/serial PK:

- Blood samples for the determination of plasma trough POS levels will be drawn on Days 3, 6, 10 (±1), 15 (±1), 22 (±1), and 28 (or the end of treatment) for PK POS evaluation.
- Additional PK samples will be drawn on Day 10 (±1) to further characterize additional PK parameters including $AUC_{0\text{-}24hr}$.
  - PK Samples for sub-group 1 Subjects: Day 10 (±1) to be collected at pre-dose, 1 hour post start of infusion, immediately before the end of infusion, approximately 15 minutes after the end of infusion, and approximate 4, 8, 12 and 24 hours post start of infusion (Detailed information please refer Trial Flow Chart, Section 6).

Subgroup 2/sparse PK:

- Blood samples for the determination of plasma trough POS levels will be drawn on Days 3, 6, 10 (±1), 15 (±1), 22 (±1), and 28 (or the end of treatment) for PK POS evaluation.

#### 4.2.3.2 Safety Endpoints

Clinical evaluations including medical history, physical examinations, weight, height, 12-lead electrocardiograms, vital signs, radiological tests and routine hematology, chemistry, and urinalysis will be performed.

Subjects will be assessed for adverse events (AEs). The rate of AE leading to discontinuation and medically significant changes in clinical laboratory tests will be listed and summarized.

Safety variables to be assessed include: AE, treatment-related AE, AE leading to discontinuation of study drug, serious adverse events (SAEs), treatment-related serious adverse events, and death. Safety will be assessed during the whole study, and serious adverse events will be reported for up to 30 days following completion of study therapy.

#### 4.2.3.3 Efficacy Endpoints

Although the main objective for this study is to evaluate pharmacokinetics from subjects at high risk for IFI, we will also observe the clinical signs and symptoms of IFI during the whole study period; the physician can also add further test if an IFI is suspected based on the signs and symptoms.

Subjects will be evaluated for the presence of a fungal infection as per standard of care during the treatment of study. Possible, probable, or proven IFI events (per EORTC/MSG version 2008 criteria) [8] will be reported on the eCRF. If a possible, proven, or probable IFI

is confirmed, or upon clinical judgment, the subject is to be discontinued from the study. Details regarding the evaluation of all clinical signs, symptoms, radiology results (e.g. CT or MRI) and other laboratory testing results (e.g. mycological results, including cytology, direct microscopy, or culture; and indirect testing, including β-D-glucan detected in serum or Galactomannan antigen detected in body fluids such as plasma, serum, bronchoalveolar lavage fluid, or cerebral spinal fluid) for the presence of a fungal infection (possible, probable, or proven IFI) should be documented. These lab tests should be pursued based on clinical judgment.

In addition, a survival assessment, if the subject is alive or dead, will be performed any day from Days 60 to 70. If the subject dies, the date of death will be recorded.

#### 4.2.3.4 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA specimens collected for future biomedical research during this clinical trial.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

### 4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

# 5.0 METHODOLOGY

## 5.1 Entry Criteria

### 5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with high risk of invasive fungal infection between the ages of 18 and 70 years (inclusive) will be enrolled in this trial.

### 5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Subject is a Chinese male or female residing in China and between 18 to 70 (inclusive) years of age at the pre-study (screening) visit.

   Female subjects of reproductive potential must demonstrate a serum β-hCG level consistent with the nongravid state at the pre-study (screening) visit and agree to use (and/or have their partner use) two (2) acceptable methods of birth control beginning at the pre-study visit throughout the study and until 30 days after the last dose of study drug. Acceptable methods of birth control two (2) of the following: intrauterine device (IUD- with or without local hormone release), diaphragm, spermicides, cervical cap, contraceptive sponge, and /or condoms. Abstinence is an alternative life style and subjects practicing abstinence may be included in the study.

   Females of non-childbearing potential between 18 to 70 (inclusive) years of age at the pre-study (screening) visit may also be enrolled. A female of non- childbearing potential is defined as:

   - A female who is postmenopausal without menses for at least 1 year and an FSH value in the postmenopausal range upon pre-study (screening) evaluation.

   and/or

   - A female who is status post hysterectomy, bilateral oophorectomy or bilateral tubal ligation.
   - Documented hysterectomy or bilateral oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Bilateral tubal ligation must be confirmed with medical records of the actual procedure otherwise the subject will be excluded. Information must be captured appropriately within the site's source documents.

2. Subject has a Body Mass Index (BMI) range of ≥15 and ≤30 kg/$m^2$ (after rounding) at the pre-study (screening) visit. BMI is calculated by taking the subject's weight in kg and dividing by the subject's height in meters, squared. The subjects should weigh ≥40 and ≤ 80 kg.
3. Each subject must have a central line catheter (Peripherally Central Venous Catheter is also acceptable) already in place as part of the standard of care for the subject's underlying disease.

4. Subject is anticipated (likely to develop within 3 days to 5 days) or documented prolonged neutropenia (absolute neutrophil count [ANC] <500/mm$^3$ [0.5 x 10$^9$/L]) at baseline and likely to last for at least 7 days due to:
    a. Standard intensive induction chemotherapy, anthracycline-based or other accepted regimen (excluding any investigational agent), for a new diagnosis of acute myelogenous leukemia (AML);
    b. Reinduction chemotherapy for AML in first relapse; or
    c. Myelosuppressive induction therapy for myelodysplastic syndromes (MDS) in transformation to AML or other diagnoses of secondary AML (therapy related, antecedent hematological disorders) other than chronic myelogenous leukemia in blast crisis
5. Each subject must be free of any clinically significant disease (other than the primary hematologic disease) that would interfere with the administration of study medication or study evaluations.
6. Each subject must be able to tolerate the administration of central IV solution medication.
7. Subject is willing to comply with the study restrictions.
8. Each subject must be willing and able to provide written informed consent for the trial. The legal representative for a subject who otherwise is unable to provide independent consent at the discretion of the investigator may provide written informed consent for the subject. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

### 5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Subject is under the age of legal consent.
2. Female subject is pregnant, or has intended to become pregnant during the study, or is nursing.
3. Subject is mentally or legally incapacitated, has significant emotional problems at the time of pre-study (screening) visit or expected during the conduct of the study or has a history of a clinically significant psychiatric disorder over the last 5 years. Subjects who have had situational depression may be enrolled in the study at the discretion of the investigator.
4. Subject has received systemic antifungal therapy (oral, intravenous, or inhaled) within 30 days of study enrollment for reasons other than antifungal prophylaxis.
5. A subject has known (including a possible, probable, or proven fungal infection per EORTC/MSG version 2008 criteria) [8] or suspected invasive or systemic fungal infection at Baseline.
6. Subject has taken posaconazole within 10 days prior to study enrollment.

7. Subject has had major surgery, donated or lost 1 unit of blood (approximately 500 mL) or participated in another investigational study within 4 weeks prior to the pre-study (screening). The 4 week window will be derived from the date of the last study procedure (i.e. post-study, AE follow-up, etc.) in the previous study to the pre-study/screening visit of the current study.
8. Subject has had a history of Type I hypersensitivity or idiosyncratic reactions to azole agents.
9. Subject has a history of significant multiple and/or severe allergies (including latex allergy), or has had an anaphylactic reaction or significant intolerability to prescription or non-prescription drugs or food.
10. Subject has had moderate or severe liver dysfunction at baseline, in this protocol defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than three times the upper limit of normal (ULN), AND a total bilirubin level greater than two times the ULN.
11. Subject with chronic active hepatitis, cirrhosis, Hepatocellular Carcinoma (HCC), or other hepatic disease caused by virus.
12. Subject has had an ECG with a prolonged QTc interval by manual reading: QTc greater than 500 msec.
13. Excluded treatments prior to specific study phases. Subject has taken one of the following drugs listed in the Table 1 below more recently than the indicated washout period prior to study treatment.
14. Excluded treatments during the study treatment period. Subject has to take one of the following drugs that are listed in Table 1 during the study.

Table 1 Prohibited Medications Prior to Start of Study Treatment and During Study Treatment

| Prohibited Medications Prior to Start of Study Treatment and During Study Treatment | Washout Period [a] |
|---|---|
| Systemic antifungal therapy (oral, intravenous or inhaled) other than study drugs for reasons other than antifungal prophylaxis. | 30 days |
| Investigational drugs (new chemical or biological entities): Investigational use of approved products or chemotherapy regimens may be permitted with the approval of the sponsor's project physician prior to use. | 30 days |
| Prophylaxis of IFI with posaconazole. | 10 days |
| Medications that are known to interact with azoles and may lead to life-threatening side effects: astemizole, cisapride, ebastine, halofantrine, pimozide, quinidine, and terfenadine. | 10 days (astemizole)<br>24 hours (others) |
| Ergot alkaloids (ergotamine, dihydroergotamine or other licensed or investigational members of this class). | 2 days |
| Medications known to lower the serum concentration/efficacy of azole antifungals: barbiturates, carbamazepine, cimetidine, isoniazid, phenytoin, rifabutin, rifampin, and St. John's Wort (hypericum perforatum). | 24 hours |
| Prophylactic use of nonabsorbable antifungal drugs: Nasal sprays of amphotericin B and aerosolized amphotericin B are prohibited. | 24 hours |
| HMG-CoA reductase inhibitors metabolized via CYP3A4 (eg, simvastatin, lovastatin, and atorvastatin). | 24 hours |
| Cyclophosphamide [b] | 24 hours |

a: These waiting times should be observed prior to start of study treatment and during study treatment in subjects receiving a prohibited drug. No concurrent use is permitted. Deviations from these washout periods must be approved by the sponsor prior to use of study drug or prohibited agent.
b: Low dose cyclophosphamide use is allowed during the treatment period with a temporary interruption of study therapy on the day of cyclophosphamide dosing.
HMG-CoA=beta-hydroxy-beta-methylglutaryl-CoA; IFI = invasive fungal infection

15. There is any concern by the investigator regarding the safe participation of the subject in the study, or for any other reason, the investigator considers the subject inappropriate for participation in the study. Subject has had any condition that, in the opinion of the investigator, may interfere with optimal participation in the study, i.e., any condition requiring the use of prohibited drugs or unstable medical conditions other than the hematological disorder such as cardiac or neurologic disorder or impairment expected to be unstable or progressive during the course of this study (e.g., seizures or demyelinating syndromes, acute myocardial infarction within 3 months of study entry, myocardial ischemia, or unstable congestive heart failure, unstable arrhythmias, atrial fibrillation with ventricular rate <60/min, or history of torsades de pointes, symptomatic ventricular or sustained arrhythmias, unstable electrolyte abnormalities [e.g., ≥ Grade 2 hypokalaemia or hypomagnesaemia]).
16. Subject has had prior enrollment in this study, or other POS studies within 90 days of study entry.
17. Subject has had an Eastern Cooperative Oncology Group (ECOG) [9] performance status >2 prior to induction chemotherapy for the subject's underlying disease.

18. Subject has had a creatinine clearance level (measured or calculated) below 50 mL/min based on the Cockcroft-Gault equation; the Cockcroft-Gault equation is as follows:

$$ClCr = \frac{(140\text{-age[yr]})(\text{body wt [kg]})*(0.85 \text{ if female})}{(72)(\text{serum creatinine [mg/dL]})}$$

*When creatinine is measured in micromole/litre, use the following formula:*

$$ClCr = \frac{(140\text{-age[yr]})(\text{body wt[kg]})*(0.85 \text{ if female})}{(72)(\text{serum creatinine [micromol/L]} \times 0.0113)}$$

19. Subject has known or suspected Gilbert's disease.
20. Subject is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

## 5.2 Trial Treatment(s)

MK-5592 IV solution to be used in this trial is outlined below in Table 2.

Table 2 Trial Treatment

| Study Drug | Dose/Potency | Dose Frequency | Route of Administration | Regimen/Treatment Period | Use |
|---|---|---|---|---|---|
| MK-5592 IV solution | 300 mg 18 mg/mL | Q12h for the first day, and QD for the rest of the IV treatment | Intravenous | IV Treatment Phase: 300 mg Q12h at Day 1 and QD at day 2 - 10 (±1) IV or Oral Treatment Phase: Day 11 (±1) to Day 28 or EOT: 300 mg QD for up to 18 (±1) days (Based on the physician's judgment) | NO control arm |
| MK-5592 oral suspension | 200 mg 40 mg/mL | 200 mg TID | Oral | Day 11 (±1) to Day 28 or EOT: 200 mg TID for up to 18 (±1) days (Based on the physician's judgment) | NO control arm |

For POS IV solution administration, dosing will occur 300 mg Q12h on Day 1 via central line administration. Subsequent dosing will be performed 300 mg once daily at approximately the same time each day.

For POS oral suspension administration, drug should be given under the guidance of physicians and local label and should be administered with food or immediately after eating (i.e., within 20 minutes). High fat meals will be recommended if applicable, since previous studies show that the exposure to POS oral suspension after a single dose was increased by about 4-fold when given with a high-fat meal compared with dosing in fasted state.

The study medication diary will be distributed to subjects when they receive oral suspension treatment and return to investigator at the visit of last dose. Medication and food information

during the POS oral suspension dosing period will be collected daily as indicated in the diary (Diary will be provided by Sponsor).

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

### 5.2.1 Dose Selection/Modification

#### 5.2.1.1 Dose Selection (Preparation)

The proposed dosing regimen of POS IV solution for the prophylaxis of invasive fungal infections is a loading dose of 300 mg Q12h on the first day, then 300 mg QD thereafter. Subject could be switched to oral suspension as 200 mg TID based on the judgment of physicians after the intensive PK samplings are completed on Day 10 (±1 day).

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

### 5.2.2 Timing of Dose Administration

MK-5592 IV solution will be administrated through central line for approximately 90 minutes, the residual volume, if any, should be documented. Subjects will have their IV infusions began at approximately the same time each day. The first three IV infusions must be given not less than 10 hours or no more than 14 hours apart. The subsequent IV infusions must be given not less than 22 hours or no more than 26 hours apart, in order to control one source of variability in drug levels. MK-5592 IV solution will be dosing without regard to food intake.

If the dosing of MK-5592 IV solution for the other days besides the day 1 is delayed, the dose of MK-5592 IV solution for the remaining days of the study should be taken following completion of the trough PK blood sampling (see flow chart for applicable study days) with at least 8 hours separating the prior day's dosing. Every attempt should be made to ensure that the subject given study medication once daily following the Q12h dosing on Day 1.

If the treatment of the subject switches to POS oral suspension at the discretion of investigator from Day 11 (±1) to Day 28 or EOT, which occurs first. For subjects in subgroup 1, the intensive PK for POS IV solution must be obtained before switching to oral suspension. The oral suspension should be given under the guidance of physicians per local label. The POS oral suspension should be administered with food or immediately after eating (i.e., within 20 minutes). The investigator may switch the subject back to POS IV solution if the subject is unable to dose with food or tolerate oral medication. Subjects who vomit within 30 minutes of POS oral administration should be given a single replacement dose as soon as possible or per guidance of the physician, following appropriate antiemetic treatment.

### 5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

### 5.3 Randomization or Treatment Allocation

Subjects participating in this trial will be allocated by non-random assignment.

### 5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

### 5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Detailed information about prohibited medication please refers Section 7.1.1.5.

### 5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

### 5.7 Diet/Activity/Other Considerations

For POS IV solution administration, there is no restriction on food intake. POS oral suspension should be administered with food or immediately after eating (i.e., within 20 minutes), and the food intake information during oral suspension dosing period will be recorded on the study medication diary. Alcohol and caffeine are prohibited on Day 10 (±1) for subject in subgroup 1.

### 5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

Discontinuation from treatment is “permanent”. Once a subject is discontinued, he/she shall not be allowed to restart treatment.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Documentation of a fungal infection (proven, probable or possible IFI) according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC-MSG version 2008) criteria [8];
- Subjects with a prolonged QTc interval on a manual measurement (QTc greater than 500 msec);
- A subject who, prior to start of study treatment and during study treatment, requires any of the prohibited medications listed in Table 1 of Section 5.1.3.

- Inability to continue to take study medication according to schedule (See Section 5.2.2 );
- Failure to comply with the dosing, evaluations, or other requirements of the study;
- A subject with liver function tests (ALT, AST, or total bilirubin) greater than 10 x ULN or other clinical or histopathologic evidence of drug-induced hepatoxicity;
- A subject who has recovered from neutropenia (ANC $\geq$500/mm$^3$) and has not considered risk factors of IFI remain at the discretion of investigator;
- The subject interrupts trial medication administration for more than 3 consecutive days;
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol;
- The subject has a confirmed positive serum pregnancy test.

## 5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

## 5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

A trial may be paused during review of newly available preclinical/clinical safety, pharmacokinetic, pharmacodynamic, efficacy or biologic data or other items of interest, prior to a final decision on continuation or termination of the trial. It may be necessary to keep the trial open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the trial. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. The overall trial end will then not be identified until the Sponsor has made the decision to end the trial following this review period. The Competent Authority(ies) and Institutional Review Board(s)/Independent Ethics Committee(s) [IRB(s)/IEC(s)] will be appraised of the maximum duration of the trial beyond the last subject out and the justification for keeping the trial open.

## 5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

## 6.0 TRIAL FLOW CHART

| | Scheduled Time | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study period | Screening | | IV Treatment Phase [a] | | | | | | | IV or Oral Treatment Phase [b] | | | Safety Follow-up [c] By Phone | Survival Assessment [d] By Phone |
| Day relative to the first dose of the study | D -14 to D -2 | D -1 | D1 | D2 | D3 | D4 | D5 | D6 | D10 (±1D) | D15 (±1D) | D22 (±1D) | D28 or EOT | D58 or EOT +30 D | Any day from D60 to D70 |
| Administrative Procedures | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | |
| Informed Consent for Future Biomedical Research [e] | X | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | | | | | | | | | |
| Subject Identification Card [f] | X | | | | | | | | | | | X | | |
| Medical History | X | | | | | | | | | | | | | |
| Prior/Concomitant Medication Review | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Documentation of Underlying Disease | X | | | | | | | | | | | | | |
| Assignment of Allocation Number | | X [g] | | | | | | | | | | | | |
| Clinic Procedures/Assessments | | | | | | | | | | | | | | |
| Physical Examination | X | X | X | | X | | | X | X | X | X | X | | |
| Height, Weight and BMI | X | | | | | | | | | | | | | |
| 12-Lead Electrocardiogram | X | X | X [h] | | | | | | X | | | X | | |
| Vital Signs (heart rate, blood pressure, respiratory rate and body temperature) [i] | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Clinical Signs and Symptoms of IFI [j] | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Radiological Tests [k] | X | X | | | | | | | X | | | X | | |
| MK-5592 (POS) Administration [l] | | | X | X | X | X | X | X | X | X | X | X | | |
| Study Medication Diary | | | | | | | | | | X [m] | X [m] | X [m] | | |
| Infusion Site Examination [n] | | | X | X | X | X | X | X | X | X | X | X | | |
| Catheter Use [o] | | | /----------X----------/ | | | | | | | | | | | |
| Adverse Events Monitoring | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Survival Assessment | | | | | | | | | | | | | | X |
| Laboratory Procedures/Assessments | | | | | | | | | | | | | | |
| Hematology / Absolute Neutrophil Count | X | | X [p] | | | | | | X | X | X | X | | |
| Urinalysis | X | | X [p] | | | | | | X | X | X | X | | |
| Chemistry | X | | X [p] | | | | | | X | X | X | X | | |

| | Scheduled Time | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study period | Screening | | IV Treatment Phase [a] | | | | | | | IV or Oral Treatment Phase [b] | | | Safety Follow-up [c] By Phone | Survival Assessment [d] By Phone |
| Day relative to the first dose of the study | D -14 to D -2 | D -1 | D1 | D2 | D3 | D4 | D5 | D6 | D10 (±1D) | D15 (±1D) | D22 (±1D) | D28 or EOT | D58 or EOT +30 D | Any day from D60 to D70 |
| Serum Pregnancy Test (Female only) | X | | X [p] | | | | | | | | | X | | |
| HIV/Hepatitis B & C Screen (per site SOP) [q] | X | | | | | | | | | | | | | |
| Blood for Future Biomedical Research [r] | | | X | | | | | | | | | | | |
| Pharmacokinetics Evaluations | | | | | | | | | | | | | | |
| Pharmacokinetic Samples (sub-group 1) [s] | | | | | X | | | X | X [t] | X | X | X | | |
| Pharmacokinetic Samples (sub-group 2) [s] | | | | | X | | | X | X | X | X | X | | |

a. POS IV solution will be administrated 300 mg Q12h on Day 1, followed by 300 mg QD on Day 2 through 10 (±1) via central line administration.
b. POS will be administrated 300 mg QD for IV solution or 200 mg TID for oral suspension at the discretion of the investigator. The investigator may switch the subject back to POS IV if the subject is unable to dose with food or tolerate oral medication. Subjects should be in hospital during the IV therapy and could be outpatients if switch to oral therapy at the discretion of investigator.
c. Subjects will be followed for 30 days for safety after last dose of study drug. Safety follow-up visit could be performed by phone.
d. Survival assessment will be performed any day form Days 60-70.
e. Future Biomedical Research is optional, subject could participate in the main trial without participating in Future Biomedical Research.
f. Issue the Subject Identification Card immediately after the subject provides written informed consent, and collects the Subject Identification Card at Day 28/EOT visit.
g. Allocation number will be assigned to the subject just after the investigator confirmed that this subject is qualified and will be enrolled in this study.
h. The ECG results at day -1 could also be accepted as day 1. ECGs need to be taken after the end of infusion during the IV therapy.
i. Vital signs should be recorded daily for hospitalized subjects and on scheduled days if outpatient. Body temperature recorded should be highest temperature (Tempmax) for each day. For screening period, daily Tempmax for 5 days prior to Day 1 should be recorded for hospitalized subjects, for outpatient, at least two temperature records from different day during Day -14 to Day -2.
j. If the physician suspects the IFIs based on the signs and symptoms, further testing (could refer EORTC/MSG version 2008 criteria) will be assessed based on the physician's judgment.
k. Per clinically indicated. Radiological testing results could be accepted if tested within 7 days; the radiology test at day -14 to day -2 occurs within 7 days before day -1, the results could also be accepted as day -1. Radiological test information could refer EORTC/MSG version 2008 criteria.
l. POS dosing will occur on every day for Day 1 through Day 28 or EOT, which occur first. For IV treatment, at least 10 (±1) days. For oral suspension administration, drug should be given under the guidance of physicians and local label and should be administered with food or immediately after eating (i.e., within 20 minutes).

| All Panels/Periods | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Scheduled Time | | | | | | | | | | | | | |
| Study period | Screening | | IV Treatment Phase [a] | | | | | | | IV or Oral Treatment Phase [b] | | | Safety Follow-up [c] By Phone | Survival Assessment [d] By Phone |
| Day relative to the first dose of the study | D -14 to D -2 | D -1 | D1 | D2 | D3 | D4 | D5 | D6 | D10 (±1D) | D15 (±1D) | D22 (±1D) | D28 or EOT | D58 or EOT +30 D | Any day from D60 to D70 |

m. The study medication diary will be distributed to subjects when they receive oral suspension treatment and return to investigator at the visit of last dose. Medication and food information during the POS oral suspension dosing period will be collected daily as indicated in the study medication diary.

n. Infusion site examination will be performed prior to dosing (0 hour) and at the end of infusion on infusion days ***and, if applicable, on days where IV Treatment is substituted for Oral Treatment due to oral tolerability issues during the Oral Treatment Phase*** for local adverse reactions. During the Oral Treatment Phase, any abnormal POS IV infusion site will continue to be inspected at all visits until resolution of the reaction and/or until Day 28 or EOT, which occur first. The infusion site will be monitored for the presence of local site reactions such as, but not limited to, tenderness, erythema, swelling, induration, or frank vein thrombosis. A record of the presence and severity of any reactions, if they occur, is to be obtained.

o. Catheter use details will be recorded daily during the IV ***administration*** and until 5 days after the end of IV therapy. Catheter type, catheter location (peripheral or central), catheter insertion and removal days, as well as the reason for the removal, will be recorded. For subject swithed to oral treatment during Day 11 (±1) to Day 28 or EOT, catheter use could be not needed.

p. Clinical laboratory tests should be drawn prior to initiation of study treatment. If the results during screenning period are within 72 hours prior medication, the results could also be accepted as Day 1 results.The results of laboratory tests should be documented. The female subject must have a negative serum beta-hCG result prior to study medication.

q. If results of these tests obtained within 3 months before screening are available, they can be used as screening.

r. Informed consent for future biomedical research testing must be provided before the DNA sample is obtained. The DNA sample should be obtained before the first drug dose on Day 1, or as soon as the informed consent and local regulatory approval for DNA collection and testing are obtained.

s. Plasma trough sampling pre-dose on Day 3, 6, 10 (±1), 15 (±1), 22 (±1) and at the end of therapy (or Day 28) for both subgroup 1 and subgroup 2. The trough sample will be taken approx. 24 hours following the previous day's dose of study drug, while before next daily dose. The actual time of all PK samples should be recorded.

t. For sub-group 1 subject, Day 10 (±1) blood samples will be collected at pre-dose, 1 hour post start of infusion, immediately before the end of infusion, approximately 15 minutes after the end of infusion, and approximate 4, 8, 12 and 24 hours post start of infusion. Blood for Pharmacokinetic assay of MK-5592 in plasma will be collected within 30 minutes for time pints pre-dose, within approximate 1 minute from time points 0-2 hours, within approximate 5 minutes from time points 2-8 hours, within approximate 10 minutes for time points 12 -24 hours, and approximate 30 minutes time points >24 hours.

# 7.0 TRIAL PROCEDURES

## 7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

### 7.1.1 Administrative Procedures

#### 7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

##### 7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

##### 7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before

performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

#### 7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

#### 7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent.

#### 7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

#### 7.1.1.5 Prior and Concomitant Medications Review

##### 7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use.

A record of all prior medication (prescription or over the counter) taken by the subject within 7 days before starting the study is to be obtained. A record of chemotherapeutic agents used for any chemotherapy regimen within 30 days of start of study treatment is to be obtained. The identity of the therapy, the dose, route, and regimen, the dates started and stopped (or notation of "continuing" if that is the case), and the reason for use are to be included in the record. Subjects receiving other antifungal agents as prophylactic therapy prior to start of study treatment should be discontinued from these treatments the day before starting study medication.

The medications, supplements, and other substances prohibited prior to start of study treatment and during study treatment are listed in Table 1.

##### 7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

Nasal sprays of amphotericin B (AMB) and aerosolized AMB are prohibited during the Treatment Phase. Topical nonabsorbable antifungal agents may be used for the treatment of mucosal or cutaneous fungal infections. Any other antifungal therapy must be administered according to the following criteria. No other systemic antifungal therapy is allowed other than study treatment.

Investigational drugs (ie, other drugs not yet approved for marketing by the Food and Drug Administration [FDA] or local health authorities) are also prohibited during the treatment phase.

POS is a potent inhibitor of CYP3A4. Coadminstration of POS with CYP3A4 substrates may result in large increases in exposure of CYP3A4 substrates. Caution is advised during co-administration of POS with CYP3A4 substrates and the dose of the CYP3A4 substrate may need to be reduced. Plasma concentrations of the CYP3A4 substrate and/or AEs should be closely monitored and the dose adjusted as needed.

Clinical and ECG monitoring (including QTc monitoring) is to be performed when the study drug is co-administered with one of the following drugs that have reported a potential risk of torsades de pointes: amiodarone, chlorpromazine, clarithromycin, domperidone, droperidol, levomethadyl, mesoridazine, methadone, erythromycin, sparfloxacin, and thioridazine.

The drugs listed below are permitted, although their efficacy and safety should be clinically monitored and/or serum levels followed with appropriate dosage adjustments as necessary at the initiation of study drug, periodically during treatment, and after discontinuation of study drug:

- Oral hypoglycemic agents
- Digoxin
- Coumadin-type anticoagulants
- Calcium channel blockers
- Theophylline
- Antiretroviral therapy (eg, efavirenz, atazanavir, or tenofovir).

Posaconazole interferes with the hepatic clearance of triazolam and midazolam, and thus, may enhance the sedative effects of these agents. Therefore, these agents are not allowed unless monitoring is provided for excessive sedation.

#### 7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

#### 7.1.1.7 Assignment of Randomization Number

Refer to “Assignment of Allocation Number” in Section 7.1.1.8.

#### 7.1.1.8 Trial Compliance (Assignment of Allocation Number/ Medication/Diet)

Each subject who meets all inclusion criteria and no exclusion criteria study will be eligible for enrollment in this study and then assigning a unique allocation number. Allocation numbers will be provided by the SPONSOR. The allocation number will never be changed and will be used to identify the patient for all procedures occurring after confirming the subject will be enrolled in this study.

Administration of trial medication will be witnessed by the investigator and/or trial staff if subjects stay in the investigative site.

When subject transfer to POS oral suspension treatment, they will be assigned a study medication diary to record the medication and food intake information during POS oral suspension dosing period.

### 7.1.2 Clinical Procedures/Assessments

Study procedures should be completed as close to the prescribed/scheduled time as possible. Procedures will be performed in the following order of proximity (below) with regard to the prescribed time. These procedures can be done prior or after the time point. For this study the blood sample for MK-5592 is the critical parameter and needs to be collected as close to the exact time point as possible.

1. Blood sample collection for MK-5592: needs to be collected as close to the exact time point as possible.
2. 12-lead ECG: need to be taken after the end of infusion during the IV therapy.

The order of priority of the rest clinical procedures can be changed with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

#### 7.1.2.1 Physical Examination

The physical examination (at Screening) will include height and weight, as well as an evaluation of the subject's medical condition. The physical examination could be repeated during the study duration at investigator's discretion.

#### 7.1.2.2 Height, Weight and BMI

Body weight and height will be obtained with the subjects' shoes off, jacket or coat removed. BMI equals a person's weight in kilograms divided by height in meters squared. (BMI=$kg/m^2$).

Note: BMI will be rounded to the nearest whole number according to the standard convention of 0.1-0.4 round down and 0.5-0.9 round up.

#### 7.1.2.3 12-Lead ECG

ECG should be performed after the end of infusion during the IV therapy. Special care must be taken for proper lead placement. Subjects may need to be shaved to ensure proper lead placement.

Subjects should be resting for at least 10 minutes prior to having ECG readings obtained. Any clinically significant abnormality must be followed until stabilization or return to Baseline.

#### 7.1.2.4 Vital Sign Measurements (Heart Rate, Blood Pressure, Respiratory Rate and Temperature)

Subjects should be resting for at least 10 minutes prior to having vital sign measurements obtained. Vital signs will include heart rate (HR), blood pressure (BP) and respiratory rate (RR). The correct size of the blood pressure cuff and the correct positioning on the subjects' arm is essential to increase the accuracy of blood pressure measurements.

The same method (e.g., manual or automated) must be used for all measurements for each individual subject and should be same for all subjects.

Body temperature will be measured with an oral, tympanic or axillary thermometer. The same method (e.g., oral, tympanic or axillary) must be used for all measurements for each individual subject and should be the same for all subjects.

#### 7.1.2.5 Clinical Signs and symptoms of IFI

Clinical signs and symptoms of IFI will be observed during the study treatment period. If the physician suspects the IFIs, further testing will be assessed based on the physician's judgment. Possible, probable, or proven IFI events (per EORTC/MSG version 2008 criteria) will be reported on the eCRF.

#### 7.1.2.6 Radiological Tests

Radiological tests will be conducted at screening, Day 10 (±1) and Day 28/EOT. Per clinically indicated, radiological testing results could be accepted if tested within 7 days; the radiology test at day -14 to day -2 occurs within 7 days before day -1, the results could also be accepted as day -1. Radiological test information could refer EORTC/MSG version 2008 criteria.

#### 7.1.2.7 Infusion Site Examination

Infusion site examination will be performed prior to dosing (0 hour) and at the end of infusion on infusion days and, if applicable, on days where IV Treatment is substituted for Oral Treatment due to oral tolerability issues during the Oral Treatment Phase for local adverse reactions. During the Oral Treatment Phase, any abnormal POS IV infusion site will continue to be inspected at all visits until resolution of the reaction and/or until Day 28 or EOT, which occur first. The infusion site will be monitored for the presence of local site reactions such as, but not limited to, tenderness, erythema, swelling, induration, or frank vein thrombosis. A record of the presence and severity of any reactions, if they occur, is to be obtained.

#### 7.1.2.8 Survival Assessment

Survival assessment, if the subject is alive or dead, will be performed any day from Days 60 to 70. If the subject dies, the date of death will be recorded.

### 7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of

the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Section 12.4.

#### 7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 3.

Table 3 Laboratory Tests

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|
| Hematocrit | Albumin | Blood | Serum β-human chorionic gonadotropin (β-hCG) |
| Hemoglobin | Alkaline phosphatase | Glucose | Hepatitis B and C (per site SOP) |
| Platelet count | Alanine aminotransferase (ALT) | Protein | HIV (per site SOP) |
| WBC (total and differential) | Aspartate aminotransferase (AST) | Specific gravity | |
| Absolute Neutrophil Count | Lactate Dehydrogenase (LDH) | Microscopic exam, if abnormal results are noted | |
| | Calcium | | |
| | Chloride | | |
| | Creatinine | | |
| | Glucose | | |
| | Phosphorus | | |
| | Potassium | | |
| | Sodium | | |
| | Total Bilirubin | | |
| | Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal | | |
| | Total protein | | |
| | Blood Urea Nitrogen (BUN or Urea, BUN is prefered) | | |

Chemistry laboratory safety tests will be performed after at least an 8-hour fast. Pre-dose laboratory procedures can be conducted up to 24 hours prior to dosing.

#### 7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

The decision as to which plasma samples collected will be assayed for evaluation of pharmacokinetics/pharmacodynamics will be collaboratively determined by the Department of Pharmacokinetics, Pharmacodynamics and Drug Metabolism and the appropriate department within Early-Stage Development/Clinical Research of MSD China. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

##### 7.1.3.2.1 Blood Collection for Plasma MK-5592

Sample collection, storage and shipment instructions for plasma samples will be provided in the appendix section 12.7.

#### 7.1.3.3 Future Biomedical Research

The following specimens are to be obtained as part of Future Biomedical Research:

- Blood for genomics use

### 7.1.4 Other Procedures

#### 7.1.4.1 Withdrawal/Discontinuation

The investigator or trial coordinator must notify the Sponsor when a subject has been discontinued/withdrawn from the trial. If a subject discontinues for any reason at any time during the course of the trial, the subject may be asked to return to the clinic (or be contacted) for a post-trial visit (approximately 30 days after the last dose of trial drug is given) to have the applicable procedures conducted. However, the investigator may decide to perform the post-trial procedures at the time of discontinuation or as soon as possible after discontinuation. If the post-trial visit occurs prior to 30 days after the last dose of trial drug is given , the investigator should perform a follow-up phone call 30 days after the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic visit. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

##### 7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

#### 7.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

#### 7.1.4.3 Domiciling

Subjects (both subgroup 1 and subgroup 2) will report to the clinical research unit (CRU) on Day -1 prior to the scheduled day of trial drug administration on Day 1 and remain in the unit during IV therapy period. Subjects could be outpatients if switch to oral therapy at the discretion of the investigator, and should come back to unit if switch back to IV therapy again judged by the investigator.

#### 7.1.4.4 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

None critical equipment was defined in this trial.

### 7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

#### 7.1.5.1 Screening

Approximately 2 weeks prior to randomization/dosing, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

#### 7.1.5.2 Treatment Period Visit

All subjects will be given a card identifying them as a participant in a research. The card will contain information detailing an appropriate contact and corresponding telephone number to be utilized in the event of an emergency.

At the discretion of the investigator, subjects will report to the clinical research unit (CRU) the day prior to the scheduled day of administration of the study drug. After pre-dose procedures have been completed and prior to the study drug administration, subjects will be assigned a subject number.

Eligibility will be confirmed at Day -1 or pre-dose through review of pregnancy test (females only), 12-lead ECG, vital signs, and concomitant medication / adverse events monitoring (see Section 6.0).

Approximately 30 subjects will be assigned to sub-group 1, and about 40 subjects will be assigned to sub-group 2.

In each sub-group, subjects will receive same regimen, only one treatment group in this study. Each subject will be receiving POS IV solution 300 mg Q12h on Day 1, followed by 300 mg QD on Day 2 through 10 (±1) via central line administration. Then, subjects will

receive IV solution 300 mg QD or oral suspension 200 mg TID for up to 18 (±1) days at the discretion of investigator. The investigator could switch the subject back to POS IV solution during oral treatment period if the subject is unable to tolerate oral suspension. The total treatment duration is at least 10 (±1) days to up to 28 days. There will be an end of treatment (EOT) visit, either at Day 28 or at the end of treatment, depends on which occur earlier.

There is no restriction on food intake for POS IV solution treatment. For POS oral suspension administration, drug should be given under the guidance of physicians per local label and should be administered with food or immediately after eating (i.e., within 20 minutes). The food intake information during oral suspension dosing period will be recorded on the diary.

PK sampling for sub-group 1 will be continued up to Day 28/ EOT. The time points for serial PK in sub-group 1 on Day 10 (±1) are pre-dose, 1 hour post start of infusion, immediately before the end of infusion, approximately 15 minutes after the end of infusion, and approximate 4, 8, 12 and 24 hours post start of infusion. The serial PK for POS IV solution on Day 10 (±1) must be obtained before switching to oral suspension. Blood samples for the determination of plasma trough POS levels will be drawn on Days 3, 6, 10 (±1), 15 (±1), 22 (±1), and 28/ EOT for PK POS evaluation.

PK sampling for sub-group 2 will only focus on trough POS levels, and be drawn on Days 3, 6, 10 (±1), 15 (±1), 22 (±1), and 28/EOT for PK POS evaluation.

During the treatment period, subjects will be instructed to report any adverse events to the investigator. Subjects may be required to remain on the CRU for longer post dose at the discretion of the Investigator.

Blood samples for plasma of MK-5592 will be drawn as close as possible to the time points provided in Section 6.0. The exact time point of blood sampling will be recorded.

Pre-dose procedures, procedures for study drug administration and post dose procedures are listed in the Study Flow Chart in Section 6.0.

#### 7.1.5.3 Post-Trial

Subjects will be required to have a follow-up phone call visit approximately 30 days after the last dose of trial drug. If the post-trial visit occurs less than 30 days after the last dose of trial drug, another follow-up phone call should be made at 30 days post the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic visit. Also, a survival assessment, if the subject is alive or dead, will be performed at any day form Days 60 to 70. If the subject dies, the date of death will be recorded. This assessment can be a phone contact visit.

#### 7.1.5.4 Critical Procedures Based on Trial Objectives: Timing of Procedure

For this trial, the blood sample for MK-5592 is the critical procedure.

At any post-dose time point, the blood sample for MK-5592 needs to be collected as close to the exact time point as possible. It is essential that the blood sample collected at the end of infusion be collected immediately before the infusion is ended. All other procedures should be completed as close to the prescribed/scheduled time as possible. Trial procedures can be performed prior or after the prescribed/scheduled time.

The order of priority can be changed during the trial with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

#### 7.1.5.5 Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameters

The dose and administration of the trial drug to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 5.8 - Subject Withdrawal/Discontinuation Criteria.

### 7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

For randomized subjects only, all adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by investigator if they are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

### 7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

The subject has taken (accidentally or intentionally) any drug administered as part of the protocol and exceeding the dose as prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

### 7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 30 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

### 7.2.3 Immediate Reporting of Adverse Events to the Sponsor

#### 7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 4 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

#### 7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be

reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

   It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

### 7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 4 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

| | | |
|---|---|---|
| **V4.0 CTCAE Grading** | **Grade 1** | **Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.** |
| | **Grade 2** | **Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.** |
| | **Grade 3** | **Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.** |
| | **Grade 4** | **Life threatening consequences; urgent intervention indicated.** |
| | **Grade 5** | **Death related to AE** |
| **Seriousness** | A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that: | |
| | †**Results in death**; or | |
| | †**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or | |
| | †**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or | |
| | †**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or | |
| | †**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or | |
| | **Is a** new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or** | |
| | **Is an overdose** (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours. | |
| | **Other important medical events** that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †). | |
| **Duration** | Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units | |
| **Action taken** | Did the adverse event cause the Sponsor's product to be discontinued? | |
| **Relationship to Sponsor's Product** | Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.<br>**The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE): | |
| | **Exposure** | Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen? |
| | **Time Course** | Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)? |
| | **Likely Cause** | Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors |

| | | |
|---|---|---|
| **Relationship to Sponsor's Product (continued)** | **The following components are to be used to assess the relationship between the test drug and the AE: (continued)** | |
| | **Dechallenge** | Was the Sponsor's product discontinued or dose/exposure/frequency reduced?<br>If yes, did the AE resolve or improve?<br>If yes, this is a positive dechallenge. If no, this is a negative dechallenge.<br>(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.) |
| | **Rechallenge** | Was the subject re-exposed to the Sponsor's product in this study?<br>If yes, did the AE recur or worsen?<br>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.<br>(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time).<br>NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL. |
| | **Consistency with Trial Treatment Profile** | Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology? |
| The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements. | | |
| **Record one of the following** | **Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).** | |
| **Yes, there is a reasonable possibility of Sponsor's product relationship.** | There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause. | |
| **No, there is not a reasonable possibility of Sponsor's product relationship** | Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.) | |

### 7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

## 8.0 STATISTICAL ANALYSIS PLAN

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of Early Development Statistics – Asia Pacific (EDS-AP), in collaboration with the Pharmacokinetics, Pharmacodynamics & Drug Metabolism, Clinical Pharmacology /China Clinical Research Departments of the Sponsor.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report (CSR).

### 8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

Individual values will be listed for the PK parameters as shown below, and the following (non-model-based) descriptive statistics will also be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 × standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 × sqrt (exp($s^2$) - 1), where $s^2$ is the observed variance on the natural log-scale). On Day 10, the PK parameters are steady-state $C_{avg}$, $AUC_{0\text{-}24hr}$, $C_{max}$, $C_{min}$ and $T_{max}$ in subgroup 1.The frequency distribution with pre-specified exposure in two categories, <500 ng/mL and ≥500 ng/mL, for steady-state $C_{avg}$ values on Day 10 in subgroup 1 will be tabulated. Descriptive statistics (mean and arithmetic percent CV) will also be tabulated for trough plasma concentrations in both subgroups by study day for MK-5592. In addition, mean trough plasma concentrations in both subgroups will be plotted by study day.

A population PK model was developed in non-Chinese healthy volunteer and patients to characterize PK and its variability after POS IV administration. Data from this study will be added to the dataset and the effect of Chinese ethnicity on the pharmacokinetics of posaconazole will be assessed. Also the percentage of the population with steady-state $C_{avg}$ ≥500 ng/mL will be estimated using the population PK model. Other necessary pharmacokinetic parameters will also be estimated from the population PK models.

### 8.2 Statistical Analysis Plan

#### 8.2.1 Hypotheses/Estimation

The pharmacokinetics parameters (e.g., steady-state Cavg, $AUC_{0\text{-}24hr}$) of POS IV solution in Chinese subjects at high risk of invasive fungal infections will be estimated. Percentage of Chinese subjects with steady-state Cavg ≥500 ng/ml will be estimated.

### 8.2.2 Analysis Endpoints

Primary key parameter for POS is steady-state $C_{avg}$. Other parameters ($C_{min}$, $C_{max}$, $T_{max}$, $AUC_{0\text{-}24\ hr}$ and CL) for POS IV administration will be determined from plasma samples taken at steady-state as described under Study Procedures.

For subgroup 1, blood samples for the determination of plasma trough POS levels will be drawn on Days 3, 6, 10 (±1), 15 (±1), 22 (±1) and 28 (or EOT) for PK POS evaluation. Additional PK samples will be drawn on Day 10 (±1) at pre-dose, 1 hour post start of infusion, immediately before the end of infusion, approximately 15 minutes after the end of infusion, and approximate 4, 8, 12 and 24 hours post start of infusion to further characterize additional PK parameters including $AUC_{0\text{-}24\ hr}$.

For subgroup 2, blood samples for the determination of plasma trough POS levels will be drawn on Days 3, 6, 10 (±1), 15 (±1), 22 (±1) and 28 (or EOT) for PK POS evaluation.

Safety endpoints will include all types of adverse experiences, in addition to laboratory safety tests, ECGs, and vital signs. Efficacy endpoints including the percentage of IFI and survival assessment can be seen in Section 4.2.3.3.

### 8.2.3 Approaches to Analyses

The following populations are defined for the analysis and reporting of data. All subjects will be reported, and their data analyzed, according to the treatment(s) they actually received.

*All Subjects as Treated (ASaT)*: All subjects who received at least one dose of the investigational drug. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP) population: The set of data generated by the subset of subjects who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol deviations. Major protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any subjects or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all subjects who are compliant with the study procedure as aforementioned and have available data from at least one treatment will be included in the primary analysis dataset. This population will be used for the PK analysis.

#### 8.2.3.1 Pharmacokinetics

Individual values will be listed for the PK parameters as shown below, and the following (non-model-based) descriptive statistics will also be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 × standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 × sqrt(exp($s^2$) - 1), where $s^2$ is the observed variance on the natural log-scale). On Day 10, the PK parameters are steady-state $C_{avg}$, $AUC_{0\text{-}24hr}$, $C_{max}$, $C_{min}$ and $T_{max}$ in subgroup 1. The frequency distribution with pre-specified exposure in two categories, <500 ng/mL and ≥500 ng/mL, for steady-state $C_{avg}$ values on Day 10 in subgroup 1 will be tabulated. Descriptive statistics (mean and arithmetic percent

CV) will also be tabulated for trough plasma concentrations in both subgroups by study day for MK-5592. In addition, mean trough plasma concentrations in both subgroups will be plotted by study day.

A population PK model was developed in non-Chinese healthy volunteers and patients to characterize PK and its variability after POS IV administration. Data from this study will be added to the dataset and the effect of Chinese ethnicity on the pharmacokinetics of posaconazole will be assessed. Also the percentage of the population with $C_{avg}$ ≥500 ng/mL will be estimated using the population PK model. Other necessary pharmacokinetic parameters will also be estimated from the population PK models.

#### 8.2.3.2 Safety

Safety will be evaluated in Chinese subjects by clinical assessment of adverse experiences and other safety parameters. Adverse experience will be listed and tabulated. Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate. Descriptive statistics will be provided for the survival assessment (any day between Days 60 and 70).

#### 8.2.3.3 Sample Size

The sample size for this study is based on overall objectives such as PK, safety and tolerability. Assuming a mean steady-state $C_{avg}$ = 1500 ng/mL and a coefficient of variation (CV) = 35%, there is a greater than 90% probability that at least 18 out of 20 evaluable subjects enrolled in subgroup 1 will have a steady-state $C_{avg}$ ≥500 ng/mL. These calculations are based on the data of steady-state pharmacokinetics from 49 subjects enrolled in an earlier study of POS IV solution (P05520, Table 5). In order to have approximately 20 evaluable subjects in subgroup 1 and considering a potential dropout rate 30%, approximately 30 subjects will be enrolled in subgroup 1. The sample size for subgroup 2 is based on prior study experience and historical requirements for filing regarding the number of subjects that would need to constitute an adequate safety database for this formulation. Therefore, we will enroll approximately 30 subjects in subgroup 1 and 40 subjects in subgroup 2.

Table 5 PK Parameters Based on Previous Studies

| Endpoint | Mean | CV | Source |
|---|---|---|---|
| $C_{avg}$ | 1500 ng/ml | 0.35 | MK-5592 PN05520 (n=49) |
| $C_{max}$ | 3280 ng/ml | 0.74 | |
| $T_{max}$ | 1.5 (0.98-4.0)[a] hr | - | |

[a] Median (minimum-maximum).

# 9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

## 9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 6.

Table 6 Product Descriptions

| Treatment Group | Product Name and Dosage Form | Dose | Potency | Total Dosage Forms | Additional Information |
|---|---|---|---|---|---|
| All (subgroup 1 and subgroup 2) | MK-5592 IV solution<br>Or<br>MK-5592 oral suspension | 300 mg/vial for IV solution<br><br>200 mg for oral suspension | 18 mg/mL for IV solution<br><br>40 mg/mL for oral suspension | 1 vial for IV solution<br><br>200 mg for oral suspension | NA |

## 9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

## 9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

## 9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

## 9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local

discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

## 10.0 ADMINISTRATIVE AND REGULATORY DETAILS

### 10.1 Confidentiality

#### 10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

#### 10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

#### 10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other

investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

### 10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

## 10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

## 10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in

conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

### 10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

### 10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

### 10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her

electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

### 10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that

contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

## 11.0 LIST OF REFERENCES

1. Dolton MH, Ray JE, Marriott D, McLachlan AJ. Posaconazole exposure-response relationship: evaluating the utility of therapeutic drug monitoring. Antimicrob Agents Chemother. 2012; 56: 2806-13.

2. Clinical Study Report of SCH 56592 P05520. Pharmacokinetics and Safety of Intravenous Posaconazole Solution Followed by Oral Posaconazole Suspension (SCH 56592) in Subjects at High Risk for Invasive Fungal Infections (Phase 1b; Protocol No. P05520).

3. Fu DX. The pharmacology of itraconazole injection and its clinical use in systemic fungal infection. Chinese Journal of New Drugs, 2004, 13: 166-168.

4. Caillot D, Bassaris H, Mcgeer A, et al. Intravenous itraconazole followed by oral itraconazole in the treatment of invasive pulmonary aspergillosis in patients with hematologic malignancies, chronic granulomatous disease, or AIDS. Clin Infect Dis, 2001, 33: 883-90.

5. Grigull L1, Kuehlke O, Beilken A, et al. Intravenous and oral sequential itraconazole antifungal prophylaxis in paediatric stem cell transplantation recipients: a pilot study for evaluation of safety and efficacy. Pediatr Transplant. 2007; 11: 261-6.

6. Liu X, Huang Y, Yang DL, et al. Prophylaxis of invasive fungal infection with different administration regimens of itraconazole in patients with acute myeloid leukemia: a report from a randomized, controlled trial. Chin J Hematol, 2013, 34: 502-506.

7. SCH56592/MK-5592 Investigator's Brochure (Version 11-Dec-2014)*.

8. Ben DP, Thomas JW, Peter DD. Revised definitions of invasive fungal disease from the European organization for research and treatment of cancer/invasive fungal infections cooperative group and the national institute of allergy and infectious diseases mycoses study group (EORTC/MSG) consensus group. CID 2008; 46: 1813-21.

9. ECOG Performance Status. http://www.ecog.org/general/perf_stat.html.

*: For those didn't list reference number.

# 12.0 APPENDICES

## 12.1 Merck Code of Conduct for Clinical Trials

**Merck***
**Code of Conduct for Clinical Trials**

**I. Introduction**

**A. Purpose**

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

**B. Scope**

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

**II. Scientific Issues**

**A. Trial Conduct**

**1. Trial Design**

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

**2. Site Selection**

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

**3. Site Monitoring/Scientific Integrity**

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

**B. Publication and Authorship**

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

**III. Subject Protection**

**A. IRB/ERC review**

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

**B. Safety**

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

**C. Confidentiality**

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

**D. Genomic Research**

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

**IV. Financial Considerations**

**A. Payments to Investigators**

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

**B. Clinical Research Funding**

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

**C. Funding for Travel and Other Requests**

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

**V. Investigator Commitment**

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

## 12.2 Collection and Management of Specimens for Future Biomedical Research

### 1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.2

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.2

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

### 2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.3 – Future Biomedical Research will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

### 3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced

to any specimens, test results, or medical information once the specimens have been rendered de-identified.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-trial's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other trial purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

If specimens are collected for a specific genotype or expression analysis as an objective to the main trial, this analysis is detailed in the main body of this protocol (**Section 8.0 – Statistical Analysis Plan**). These specimens will be processed, analyzed, and the remainder of the specimen will be destroyed. The results of these analyses will be reported along with the other trial results. A separate specimen will be obtained from properly-consented subjects in this protocol for storage in the biorepository for Future Biomedical Research.

**4. Confidential Subject Information for Future Biomedical Research**

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which

does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

**5. Biorepository Specimen Usage**

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

**6. Withdrawal From Future Biomedical Research**

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact Merck using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided by Merck to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from Merck to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

**7. Retention of Specimens**

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

**8. Data Security**

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

## 9. Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all trial sites who participated in the Merck clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

## 10. Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

## 11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

Merck has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it

be released to outside persons or agencies, in any way that could be tied to an individual subject.

**12. Self-Reported Ethnicity**

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

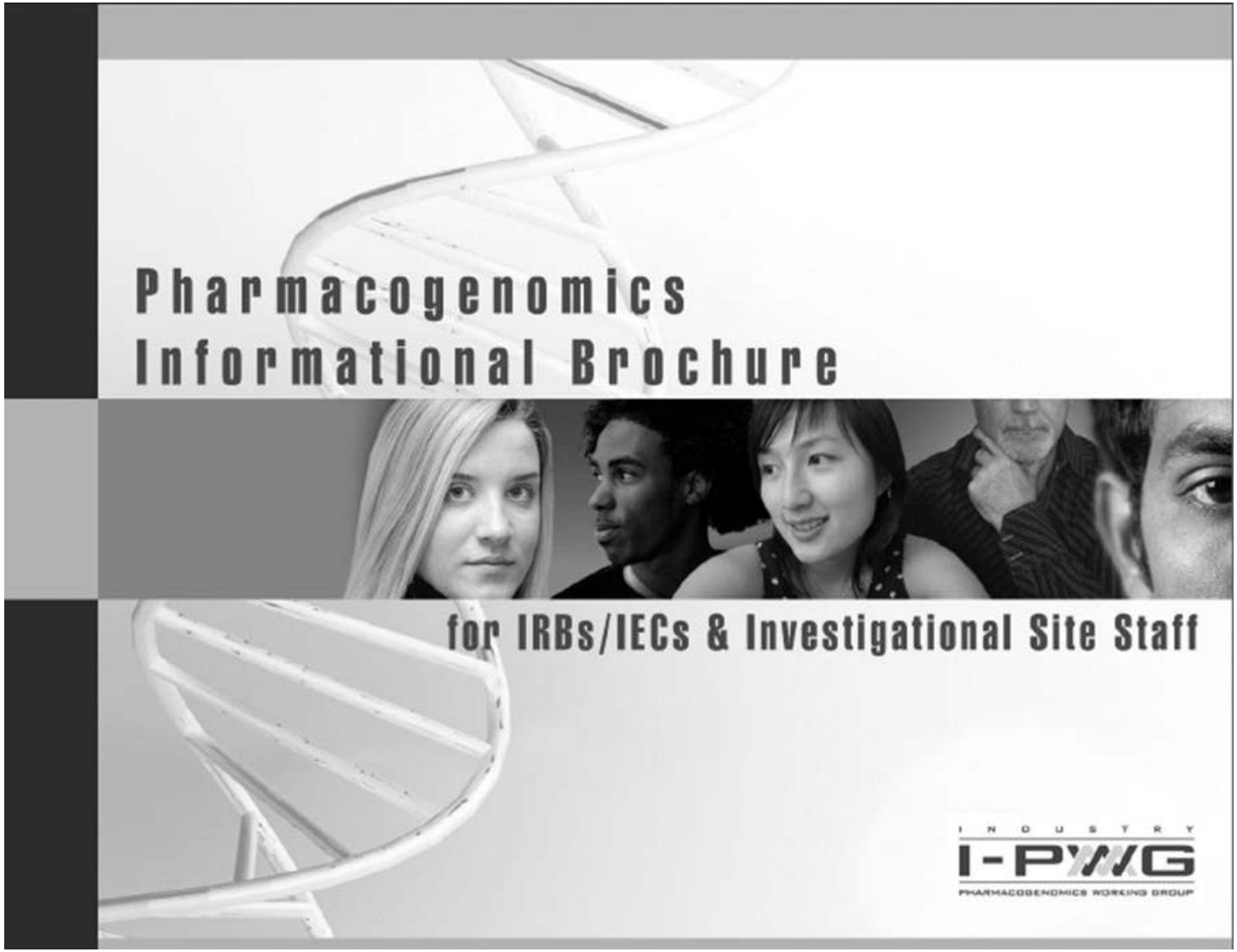
**13. Questions**

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

**14. References**

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

### 12.3 Pharmacogenetics Informational Brochure for IRBs/IECs & Investigational Site Staff



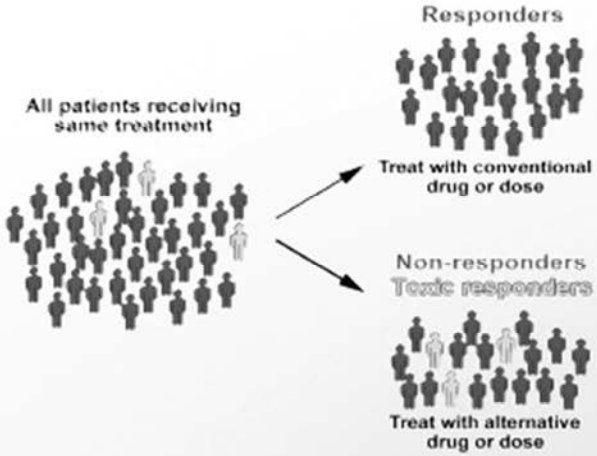
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

*Developed by*
*The Industry Pharmacogenomics Working Group (I-PWG)*
***www.i-pwg.org***

## What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid** (**DNA**). DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

**Pharmacogenomics (PGx)** is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA[1], and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.




## Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

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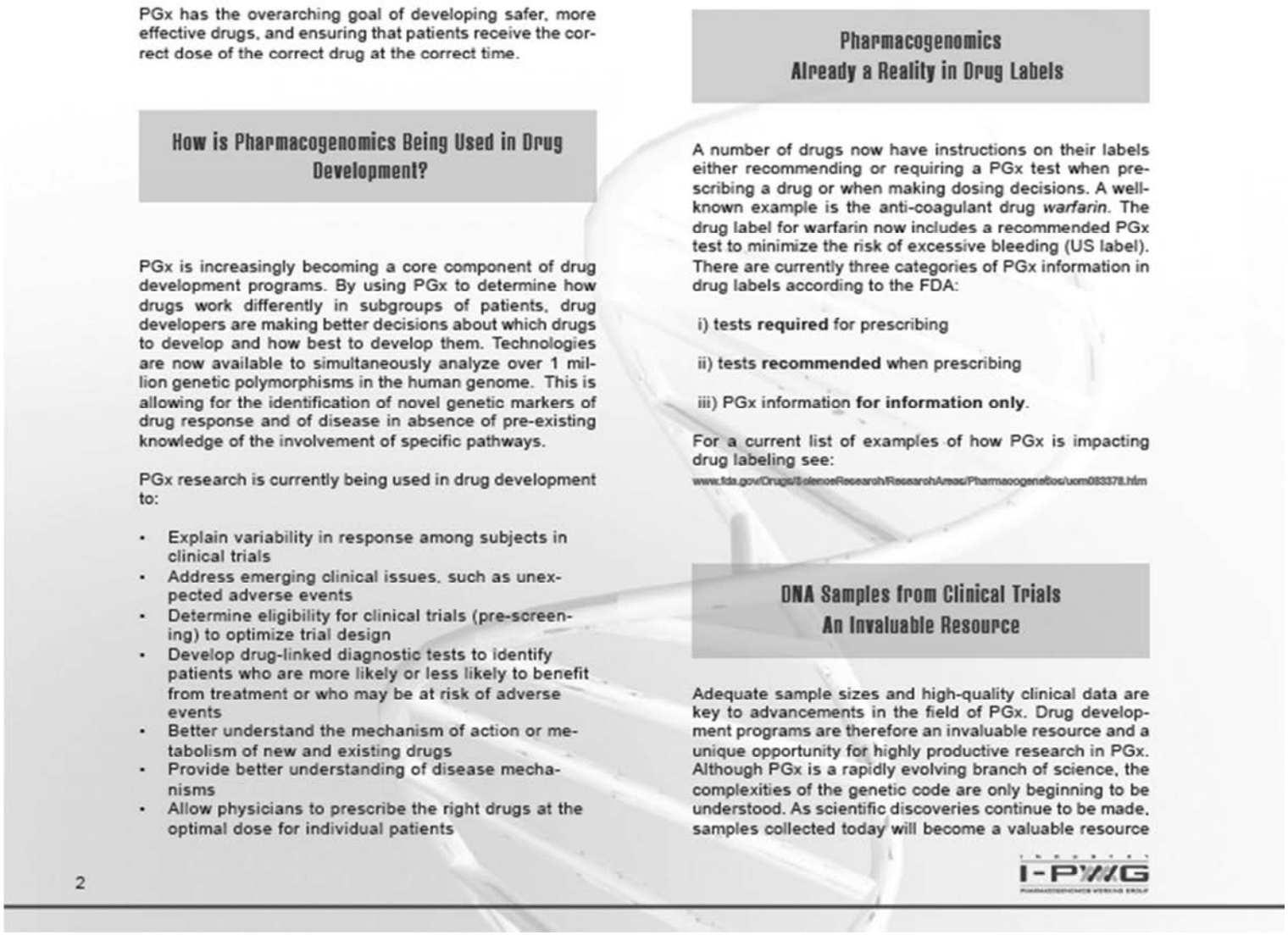
PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.
How is Pharmacogenomics Being Used in Drug Development?
PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.
PGx research is currently being used in drug development to:
• Explain variability in response among subjects in clinical trials
• Address emerging clinical issues, such as unexpected adverse events
• Determine eligibility for clinical trials (pre-screening) to optimize trial design
• Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
• Better understand the mechanism of action or metabolism of new and existing drugs
• Provide better understanding of disease mechanisms
• Allow physicians to prescribe the right drugs at the optimal dose for individual patients
2
Pharmacogenomics
Already a Reality in Drug Labels
A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug warfarin. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:
i) tests required for prescribing
ii) tests recommended when prescribing
iii) PGx information for information only.
For a current list of examples of how PGx is impacting drug labeling see:
www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
DNA Samples from Clinical Trials
An Invaluable Resource
Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource
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for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

## Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies[2]. These elements build upon existing basic elements of informed consent for clinical research on human subjects[3].

## Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006[4].

## Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

**i) Sample Labeling**

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15[1]. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)[1]. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

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Table adapted from ICH Guidance E15

| Sample Coding Category | | Link Between Subject's Personal Identifiers and Genomic Biomarker Data | Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request | Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data | Extent of Subject's Confidentiality and Privacy Protection |
|---|---|---|---|---|---|
| Identified | | Yes (Direct)<br>Allows for Subjects to be Identified | Yes | Yes | Similar to General Healthcare Confidentiality and Privacy |
| Coded | Single | Yes (Indirectly)<br>Allows for Subjects to be Identified (via Single, Specific Coding Key) | Yes | Yes | Standard for Clinical Research |
| | Double | Yes (Very Indirectly)<br>Allows for Subjects to be Identified (via the Two Specific Coding Keys) | Yes | Yes | Added Privacy and Confidentiality Protection over Single Code |
| Anonymized | | No<br>Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted | No | No | Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted |
| Anonymous | | No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified | No | No | Genomic Data and Samples Never Linked to Subject |

**ii) Separation of Data and Restricted Access**

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form[2].

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iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)[5, 6] serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: http://www.i-pwg.org

## Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

## Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: http://www.i-pwg.org. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[19].

## Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: http://www.i-pwg.org.

## What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: http://www.i-pwg.org.

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## Glossary

**Identified Data and Samples:** Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). The use of identified data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

**Coded Data and Samples:** Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.

***Single-Coded Data and Samples:*** are usually labeled with a single specific code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

***Double-Coded (De-identified) Data and Samples:*** are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code.

**Anonymized Data and Samples:** Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification.

**Anonymous Data and Samples:** Anonymous data and samples are never labeled with personal identifiers when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

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## References

1. ICH E15 - Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)

2. Anderson DC, Gomez-Mancilla B, Spear BB, et al. Elements of informed consent for pharmacogenetic research; perspective of the pharmacogenetics working group. Pharmacogenomics Journal 2002;2(5):284-92.

3. ICH E6(R1) - Guideline for Good Clinical Practice. June 1996. (Accessed at: http://www.ich.org/LOB/media/MEDIA482.pdf)

4. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2006;20(1):24-36.

5. Genetic Information Nondiscrimination Act (GINA): 2007-2008. (Accessed at: http://www.genome.gov/24519851)

6. Hudson KL, Holohan MK, Collins FS. Keeping pace with the times--the Genetic Information Nondiscrimination Act of 2008. New England Journal of Medicine 2008;358(25):2661-3.

7. EMEA CHMP Reflection Paper on Pharmacogenomics in Oncology - Draft. 2008. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/12843506endraft.pdf)

8. EMEA CHMP Position Paper on Terminology in Pharmacogenetics. June 2003. (Accessed at: http://www.tga.health.gov.au/docs/pdf/euguide/emea/307001en.pdf)

9. EMEA CHMP Reflection Paper on the Use of Pharmacogenetics in the Pharmacokinetic Evaluation of Medicinal Products. May 2007. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogentics/12851706enfin.pdf)

10. EMEA CHMP Guideline on Pharmacogenetic Briefing Meetings. November 2006. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/2022704en.pdf)

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11. EMEA CHMP Reflection Paper on Pharmacogenomic Samples, Testing, and Data Handling. November 2007. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/20191406en.pdf)

12. EMEA CHMP Reflection Paper on the Use of Genomics in Cardiovascular Clinical Intervention Trials. November 2007. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/27878906enfin.pdf)

13. EMEA CHMP Biomarkers Qualification: Guidance to Applicants. 2008. (Accessed at: http://www.emea.europa.eu/pdfs/human/biomarkers/7289408en.pdf)

14. EMEA CHMP Understanding Terminology Used in Pharmacogenetics July 2004. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/384204en.pdf)

15. FDA Companion Guidance - Pharmacogenomic Data Submissions - draft. August 2007. (Accessed at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079855.pdf)

16. FDA. FDA Guidance - Pharmacogenetic Tests and Genetic Tests for Heritable Markers. June 2007. (Accessed at: www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077862.htm)

17. FDA Guidance - Pharmacogenomic Data Submissions. March 2005. (Accessed at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126957.pdf)

18. EMEA FDA - Processing Joint FDA EMEA VGDSs within the framework of the Confidentiality Arrangement May 2006. (Accessed at : http://www.emea.europa.eu/pdfs/general/direct/pr/FDAEMEA.pdf)

19. Rittenhouse P. Framing DNA collection in the clinic. Biocentury, The Bernstein Report on BioBusiness March 2006:A13-5.



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http://www.i-pwg.org

## 12.4 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

| | Pre-trial | Treatment Periods | Post-trial | Total Collections | mL Per Collection | Total mL/ Test |
|---|---|---|---|---|---|---|
| Laboratory safety tests | 1 | 5 | | 6 | 10 | 60 |
| HIV/Hepatitis Screen (at the discretion of the investigator) | 1 | | | 1 | 4 | 4 |
| Blood for Future Biomedical Research | | 1 | | 1 | 8.5 | 8.5 |
| Blood for pregnancy | 1 | 2 | | 3 | 4 | 12 |
| Blood for MK-5592 for Sub-group 1 only | | 13 | | 13 | 4 | 52 |
| Blood for MK-5592 for Sub-group 2 only | | 6 | | 6 | 4 | 24 |
| Total Blood Volume Per Subject sub-group 1 /Sub-group 2[†] | | | | | | 136.5/108.5 mL |

[†] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL

## 12.5 Algorithm for Assessing Out-of-Range Laboratory Values

For all laboratory values obtained at pre-study (screening) visit evaluation:

A. If all protocol-specified laboratory values are normal, the subject may enter the study.

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the subject will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

1. The subject may be excluded from the study;
2. The subject may be included in the study if the abnormal value(s) is not clinically significant (NCS) (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).
3. The subject may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (e.g., elevated eosinophil count in a subject with asthma or seasonal allergies) (this should be annotated on the laboratory report) or
4. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).
    a. If the repeat test value is within the normal range, the subject may enter the study.
    b. If the repeat test value is still abnormal, the study investigator will evaluate the potential subject with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the subject may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the Subject will be excluded from the study.

## 12.6 POS IV Solution Preparation and Administration

The procedure described below is only a draft procedure. It may be altered after the site performing the procedure has evaluated it. Any alterations will be documented.

This is an unblinded study in which the investigator, sponsor and subjects know the treatment. Therefore, POS IV vials will be packaged open-label and sent directly to the research staff.

**Storage**

POS IV solution should be kept at 2°C to 8°C until ready for use. DO NOT FREEZE.

**Treatment Preparation and Administration**

- POS IV Solution will be diluted with 5% dextrose in water or sodium chloride 0.9%. POS IV solution should only be administered with these diluents. Use of other infusion solutions may result in particulate formation.
- Subjects will have their IV infusions began at approximately the same time each day. The first three IV infusions must be given not less than 10 hours or no more than 14 hours apart. The subsequent IV infusions must be given not less than 22 hours or no more than 26 hours apart.
- Administer via a central venous line, including peripherally central venous catheter (PICC) or a dedicated lumen of a central venous catheter (CVC) by slow infusion over approximately 90 minutes. POS IV solution is not for bolus administration.
- If any problems occur with the pump, tubing or cannulae during treatment administration, the research staff must be the only member of staff who resolves the issue. The study center must be prepared with replacement supplies so as not to interrupt the study drug infusion. The research staff must be available throughout IV treatment administration.
- All POS IV vials, used and unused, must be retained for drug accountability.

**Preparation**

1. Equilibrate the refrigerated vial of POS IV solution to room temperature.
2. Gently invert the vial 10 times and aseptically transfer 16.7 mL (18 mg/mL, 1 vial) of POS IV solution to an intravenous bag containing approximately 133.3 mL of 5% dextrose in water or sodium chloride 0.9%. NOTE: The final volume of the bag should be 150 mL.
3. Gently invert the intravenous bag containing the POS IV solution 10 times.
4. POS IV solution is a single dose sterile solution without preservatives. Once admixed, the product should be used immediately. If not used immediately, the solution can be stored up to 24 hours refrigerated 2-8°C (36-46°F). This medicinal product is for single use only and any unused solution should be discarded.
5. Parenteral drug products should be inspected visually for particulate matter prior to administration, whenever solution and container permit. Once admixed, the solution of Noxafil ranges from colorless to yellow. Variations of color within this range do not affect the quality of the product.

**Administration**

1. Prime IV tubing completely with 5% dextrose in water or sodium chloride 0.9%.
2. Remove the covering on the port of the POS admixture IV bag and insert the solution set into the appropriate port.
3. If the standard solution set does not contain a 0.22 micron or less filter, then one must be attached at the end of the solution set.
4. Hang the POS admixture IV bag on one IV pole vertically.
5. Thread the primed IV tubing through the pump.
6. Connect the IV tubing to the central venous catheter that is inserted into the subject's vein.
7. Program the pump to deliver the contents of the bag in approximately 90 minutes (follow instructions supplied in the manual for the pump).
8. Start the pump and infuse the entire contents of the POS admixture.
9. Flush the line according to guidelines for local standard of care for central catheters after intermittent infusions using 25 mL of 5% dextrose in water or sodium chloride 0.9%. No drug should be added to this 25 mL. Complete the flushing over a period no less than 2 minutes and no more than 15 minutes.
10. Dispose of the IV bags and solution set according to the hospital's Hazardous/Medical Waste policy.

## 12.7 MK-5592 Plasma Assays—Sample Collection, Handling, Labeling, Storage, and Shipment

The following sample handling instruction is an example. Please consult Drug Metabolism/Pharmacokinetics (DMPK) and sample analysis laboratory for MK-5592 information on MK-5592 blood sample collection, handling, storage and shipment.

**PK Sample Collection and Processing Procedure for MK-5592**

**Method LCMSC 549**

**Human Plasma (K2EDTA)**

For specific time points of sample collection, please refer to the Study Flow Chart (Section 6.0).

One (1) 4 mL Vacutainer tube (lavender top, 13 x 75 mm, spray coated K2EDTA, BD Vacutainer # 367844 or equivalent) will be collected for PK analysis at each of the time points specified in the clinical protocol. Fill tube as completely as possible to ensure sufficient sample volume for the required tests.

Immediately after the sample is drawn, gently invert the tube 8 to 10 times to thoroughly mix the anticoagulant and place the tube in a cryoblock (in an upright position) or in an ice water mixture to the approximate height of the blood in the tube. (Samples can be stored cold for up to 30 minutes prior to centrifugation.) Centrifuge the sample under refrigeration 2 ºC to 8 ºC at 2500 to 3000 rpm (approximately 650 to 1450 x g) for 10 to 15 minutes to achieve a clear plasma layer over the red cells (the speed and time may be varied according to the make and model of centrifuge used). Immediately transfer the plasma to a properly labeled polypropylene sample storage tube, cap and freeze samples at -20 ºC until shipment. Samples should be place in freezer within 60 minutes after sample collection.

**Sample Labeling**

1. Whole Blood Samples. Vacutainers containing whole blood should be labeled (non-bar-coded) as appropriate.
2. Plasma Samples. Tubes containing plasma samples should be labeled with the pre-printed bar-coded labels with the allocation number, day, date and time (hours post-dose) provided by the Sponsor. Labels should be placed on the tubes toward the top 30% of the tube in order for the level of plasma in the tube to be viewed. Only **one (1)** layer of label should be placed on the tube (not 2). This is critical for the proper functioning of the automated liquid handling station.

**Sample Shipment**

- Only the plasma samples need to be shipped to the central lab and all the remaining full blood samples could be destroyed at study site.
- All sample shipments should be preceded by a phone call or fax prior to their receipt. All HIV positive or other known infectious sample shipments must be preceded by a phone call or facsimile prior to their receipt.
- Detailed sample inventory information must accompany the samples. Lack of paperwork or illegible information will delay sample login and project initiation. Samples that are

unclearly or incompletely labeled may be subject to additional handling fees. Submission of sample inventory information in electronic form is encouraged.

- Frozen samples should be shipped via overnight courier with an adequate amount of dry ice Monday through Friday to the following:

Note: Sample storage for this study is -20ºC.

## 12.8 Defining Opportunistic Invasive Fungal Infections (European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group, National Institute of Allergy and Infectious Diseases Mycoses Study Group)

MAJOR ARTICLE

# Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group

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***Background.*** Invasive fungal diseases are important causes of morbidity and mortality. Clarity and uniformity in defining these infections are important factors in improving the quality of clinical studies. A standard set of definitions strengthens the consistency and reproducibility of such studies.

***Methods.*** After the introduction of the original European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group definitions, advances in diagnostic technology and the recognition of areas in need of improvement led to a revision of this document. The revision process started with a meeting of participants in 2003, to decide on the process and to draft the proposal. This was followed by several rounds of consultation until a final draft was approved in 2005. This was made available for 6 months to allow public comment, and then the manuscript was prepared and approved.

***Results.*** The revised definitions retain the original classifications of "proven," "probable," and "possible" invasive fungal disease, but the definition of "probable" has been expanded, whereas the scope of the category "possible" has been diminished. The category of proven invasive fungal disease can apply to any patient, regardless of whether the patient is immunocompromised, whereas the probable and possible categories are proposed for immunocompromised patients only.

***Conclusions.*** These revised definitions of invasive fungal disease are intended to advance clinical and epidemiological research and may serve as a useful model for defining other infections in high-risk patients.

In 2002, a consensus group of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) published standard definitions for invasive fungal infections for clinical and epidemiological research [1]. These definitions were developed to facilitate the identification of reasonably homogeneous groups of patients for clinical and epidemiologic research, to help design clinical trials to evaluate new drugs and management strategies, and, last but not least, to foster communication between

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international researchers. The definitions assigned 3 levels of probability to the diagnosis of invasive fungal infection that develops in immunocompromised patients with cancer and in hematopoietic stem cell transplant recipients—namely, "proven," "probable," and "possible" invasive fungal infection. The definitions established a formal framework for defining invasive fungal infection with a variable certainty of diagnosis. Proven invasive fungal infection required only that a fungus be detected by histological analysis or culture of a specimen of tissue taken from a site of disease; in the case of *Cryptococcus neoformans*, detection of capsular antigen in CSF or a positive result of an India ink preparation of CSF was considered sufficient to establish a diagnosis of proven cryptococcosis. By contrast, probable and possible invasive fungal infections hinged on 3 elements—namely, a host factor that identified the patients at risk, clinical signs and symptoms consistent with the disease entity, and mycological evidence that encompassed culture and microscopic analysis but also indirect tests, such as antigen detection. These EORTC/MSG Consensus Group definitions have been used in major trials of antifungal drug efficacy, in strategy trials [2–6], for the formulation of clinical practice guidelines [7], for validation of diagnostic tests [8–13], and for performance of epidemiologic studies [14].

The previously published definitions were not without their shortcomings. For instance, the original category of possible invasive fungal infection allowed too many dubious cases to be included, particularly those involving neutropenia, nonspecific pulmonary infiltrates, and persistent fever refractory to broad-spectrum antibiotics but with no evidence of invasive fungal infection [15]. These cases may represent patients at higher risk of invasive fungal infection but are quite different from the cases, also defined as possible cases, for which more specific pulmonary abnormalities, such as a halo or air-crescent sign characteristic of invasive aspergillosis, were present. Indeed, the definitions were modified to allow enrollment of similar cases into clinical trials, because they are considered to represent likely invasive fungal disease even without supporting mycological evidence [2, 16]. This pragmatic approach solved the problem of recruitment of representative cases, but it clearly highlighted the need to refine further the definitions, to distinguish dubious cases from the more likely cases when mycological evidence was not forthcoming. The growing body of evidence regarding the value of high-resolution CT of chest and abdomen [17] and of indirect diagnostic tests—such as the detection of galactomannan in body fluids other than serum and plasma, of $\beta$-D-glucan in serum, and of fungal DNA in body fluids by PCR—provided additional incentive to review the definitions [18, 19]. The original definitions were also restricted to patients with cancer and to recipients of hematopoietic stem cell transplants; however, invasive fungal infections are known to affect other populations, including recipients of solid-organ transplants and patients with primary immunodeficiencies (e.g., chronic granulomatous disorder) [20, 21]. Finally, it was considered appropriate to explore the possibility of formulating specific criteria for diseases caused by less common fungal pathogens.

## REVISION PROCESS

The EORTC/MSG Consensus Group met in Chicago, Illinois, on 14 September 2003 during the 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and included 13 members from the EORTC and 17 from the MSG. J. Powers also participated for the US Food and Drug Administration (FDA), and there were 5 observers from 4 pharmaceutical companies (J. Rex [Astra Zeneca], C. Sable [Merck], M. Bresnik [Gilead], and G. Triggs and A. Baruch [Pfizer]). B.d.P. and T.J.W. were confirmed as joint chairs, and J.P.D. was designated as secretary for the group. Three subcommittees were appointed to prepare proposals for mold infection, candidiasis, and endemic mycoses. The proposals were collated by the secretary, who integrated them into a general framework. They were then circulated by electronic mail to all group members. The ensuing comments again were centrally combined for a subsequent round of electronic consultation. The remaining issues that appeared difficult to solve by the electronic route were addressed in open meetings during the 15th European Congress of Clinical Microbiology and Infectious Disease in Copenhagen, Denmark, and the 45th Annual ICAAC in Washington, DC. A majority vote was decisive when a consensus among the members could not be achieved. The final draft was made available to the wider community for comment at the Doctor Fungus Web site [22] and The Aspergillus Web site [23]. Thereafter, the manuscript was prepared and was circulated among all group members for their final approval.

At the first meeting, all group members agreed to the need to refine and revise the definitions. It was also agreed unanimously that the definition set should remain easily reproducible and should offer the opportunity for a reasonable comparison of future data sets with data sets that had been collected in clinical trials that involved patients with proven and probable invasive fungal infections according to the original definitions. Finally, the group set out to reexamine the feasibility of using the definitions for treatment purposes, to devise a means of extending their applicability to other patient groups, to review the relevance of the findings obtained from studies based on the definitions for clinical practice, and to attempt to incorporate all the available laboratory tests and imaging techniques into the definitions.

## REVISED DEFINITIONS

The term "invasive fungal disease" (IFD) was adopted to reflect more accurately the notion that we are dealing with a disease process caused by fungal infection. An adequate diagnostic evaluation of the infectious disease process, to exclude an alternative etiology, was deemed to be a necessary prerequisite to classify it as an IFD. The group reaffirmed that the definitions should be used only to assist in research and that the integrity of the original definitions with the classifications of proven, probable, and possible IFD would be preserved (tables 1–3). Infections caused by *Pneumocystis jiroveci* are not included. The criteria for proven and probable IFD (tables 1 and 2) were modified to reflect advances in indirect tests, whereas the category of possible IFD (table 3) was revised to include only cases that are highly likely to be caused by a fungal etiology, although mycological evidence is lacking. Hence, the definitions of probable and possible IFD were based on the same 3 elements as were the original definitions: host factors, clinical manifestations, and mycological evidence.

Host factors are not synonymous with risk factors but are characteristics by which individuals predisposed to acquire IFD can be recognized. Consequently, the presence of fever was removed as a host factor because it represents a clinical feature, not a host factor, and is nonspecific for IFD. The host factors were extended to receipt of a solid-organ transplant, hereditary immunodeficiencies, connective tissue disorders, and receipt of immunosuppressive agents—for example, corticosteroids or T cell immunosuppressants, such as calcineurin inhibitors, anti–TNF-$\alpha$ drugs, anti-lymphocyte antibodies, or purine analogues. The distinction between "minor" and "major" clinical criteria was abandoned in favor of more-characteristic and objectively verifiable evidence, such as the findings on medical imaging that indicated a disease process consistent with IFD by use of a standardized glossary of definitions. For example, in the case of chest CT imaging to categorize pulmonary lesions, the vast majority of immunocompromised patients with invasive pulmonary aspergillosis have focal rather than diffuse pulmonary infiltrates and present with at least 1 macronodule, with or without a halo sign [24]. These infections can also manifest as wedge-shaped infiltrates and segmental or lobar consolidation. Although none of the imaging findings is pathognomonic for IFD, the observation that, in the appropriate patient population, the outcome of antifungal therapy did not differ between febrile patients with nodular lesions and patients with mycological evidence of an IFD supports the use of this clinical criterion [17]. A similar consideration applies to patients with lesions on CT or ultrasound that are regarded as typical for chronic disseminated candidiasis. In the original definitions, patients with such lesions were defined as having probable hepatosplenic candidiasis without any need for mycological support. In the revised definitions, such cases are classified as possible IFD, thereby retaining the consistency of the definitions and preserving the distinction between probable IFD and possible IFD. For a patient with appropriate host factors and clinical evidence of pulmonary disease, bronchoalveolar lavage fluid that yields *Aspergillus*, Zygomycetes, *Fusarium*, or *Scedosporium* species or other pathogenic molds would constitute mycological support and would allow the case to be classified as probable pulmonary IFD.

As with the original definitions, indirect tests were considered for inclusion only if they were validated and standardized. Furthermore, because commercial tests for diagnostic use had to provide criteria for interpretation to gain approval, it was decided to rely entirely on the thresholds recommended by the manufacturer. On the basis of recent studies, the Platelia *Aspergillus* galactomannan EIA could be applied to CSF and bronchoalveolar lavage fluid, as well as plasma and serum. The $\beta$-D-glucan assay also was included as a marker for probable IFD, because this test detects other species of fungi besides *Aspergillus*, and a commercial test for it (Fungitell assay; Associates of Cape Cod) has been approved by the FDA. By contrast, molecular methods of detecting fungi in clinical specimens, such as PCR, were not included in the definitions because there is as yet no standard, and none of the techniques has been clinically validated.

## THE CATEGORIES

***Proven IFD.*** There was general agreement that the category of proven IFD should be retained, requiring proof of IFD by demonstration of fungal elements in diseased tissue for most conditions (table 1). Revisions were made to this category to reflect advances in indirect assays that are highly specific for the infection being detected. By its very nature, this category is likely to be valid irrespective of host factors or clinical features. Individual IFD entities—for example, proven aspergillosis—require culture and identification. Failing this, the disease is designated as proven mold IFD (table 1). The histological appearance of the endemic dimorphic fungi, *Histoplasma capsulatum*, as small intracellular budding yeasts; *Coccidioides* species as spherules; *Paracoccidioides brasiliensis* as large yeasts with multiple daughter yeasts in a "pilot-wheel configuration"; and *Blastomyces dermatitidis* as thick-walled, broad-based budding yeasts is sufficiently distinctive to permit a definitive diagnosis (table 3). *H. capsulatum* variety *capsulatum* resembles *Candida glabrata* or *Leishmania* species in tissue but can be distinguished from them by characteristic histological features of granulomatous inflammation in histoplasmosis in some patient groups and by staining with silver, which shows staining for the fungi but not for *Leishmania* species.

The category of proven IFD was modified to reflect advances

**Table 1. Criteria for proven invasive fungal disease except for endemic mycoses.**

| Analysis and specimen | Molds[a] | Yeasts[a] |
|---|---|---|
| Microscopic analysis: sterile material | Histopathologic, cytopathologic, or direct microscopic examination[b] of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage | Histopathologic, cytopathologic, or direct microscopic examination[b] of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast cells—for example, *Cryptococcus* species indicated by encapsulated budding yeasts or *Candida* species showing pseudohyphae or true hyphae[c] |
| Culture | | |
| Sterile material | Recovery of a mold or "black yeast" by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding bronchoalveolar lavage fluid, a cranial sinus cavity specimen, and urine | Recovery of a yeast by culture of a sample obtained by a sterile procedure (including a freshly placed [<24 h ago] drain) from a normally sterile site showing a clinical or radiological abnormality consistent with an infectious disease process |
| Blood | Blood culture that yields a mold[d] (e.g., *Fusarium* species) in the context of a compatible infectious disease process | Blood culture that yields yeast (e.g., *Cryptococcus* or *Candida* species) or yeast-like fungi (e.g., *Trichosporon* species) |
| Serological analysis: CSF | Not applicable | Cryptococcal antigen in CSF indicates disseminated cryptococcosis |

[a] If culture is available, append the identification at the genus or species level from the culture results.
[b] Tissue and cells submitted for histopathologic or cytopathologic studies should be stained by Grocott-Gomori methenamine silver stain or by periodic acid Schiff stain, to facilitate inspection of fungal structures. Whenever possible, wet mounts of specimens from foci related to invasive fungal disease should be stained with a fluorescent dye (e.g., calcofluor or blankophor).
[c] *Candida*, *Trichosporon*, and yeast-like *Geotrichum* species and *Blastoschizomyces capitatus* may also form pseudohyphae or true hyphae.
[d] Recovery of *Aspergillus* species from blood cultures invariably represents contamination.

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**Table 2. Criteria for probable invasive fungal disease except for endemic mycoses.**

| |
|---|
| Host factors[a] |
| Recent history of neutropenia [<0.5 × $10^9$ neutrophils/L [<500 neutrophils/$mm^3$] for >10 days] temporally related to the onset of fungal disease |
| Receipt of an allogeneic stem cell transplant |
| Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks |
| Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days |
| Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency) |
| Clinical criteria[b] |
| Lower respiratory tract fungal disease[c] |
| The presence of 1 of the following 3 signs on CT |
| Dense, well-circumscribed lesion(s) with or without a halo sign |
| Air-crescent sign |
| Cavity |
| Tracheobronchitis |
| Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis |
| Sinonasal infection |
| Imaging showing sinusitis plus at least 1 of the following 3 signs |
| Acute localized pain (including pain radiating to the eye) |
| Nasal ulcer with black eschar |
| Extension from the paranasal sinus across bony barriers, including into the orbit |
| CNS infection |
| 1 of the following 2 signs |
| Focal lesions on imaging |
| Meningeal enhancement on MRI or CT |
| Disseminated candidiasis[d] |
| At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks |
| Small, target-like abscesses (bull's-eye lesions) in liver or spleen |
| Progressive retinal exudates on ophthalmologic examination |
| Mycological criteria |
| Direct test (cytology, direct microscopy, or culture) |
| Mold in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples, indicated by 1 of the following |
| Presence of fungal elements indicating a mold |
| Recovery by culture of a mold (e.g., *Aspergillus*, *Fusarium*, Zygomycetes, or *Scedosporium* species) |
| Indirect tests (detection of antigen or cell-wall constituents)[e] |
| Aspergillosis |
| Galactomannan antigen detected in plasma, serum, bronchoalveolar lavage fluid, or CSF |
| Invasive fungal disease other than cryptococcosis and zygomycoses |
| β-D-glucan detected in serum |

**NOTE.** Probable IFD requires the presence of a host factor, a clinical criterion, and a mycological criterion. Cases that meet the criteria for a host factor and a clinical criterion but for which mycological criteria are absent are considered possible IFD.

[a] Host factors are not synonymous with risk factors and are characteristics by which individuals predisposed to invasive fungal diseases can be recognized. They are intended primarily to apply to patients given treatment for malignant disease and to recipients of allogeneic hematopoietic stem cell and solid-organ transplants. These host factors are also applicable to patients who receive corticosteroids and other T cell suppressants as well as to patients with primary immunodeficiencies.

[b] Must be consistent with the mycological findings, if any, and must be temporally related to current episode.

[c] Every reasonable attempt should be made to exclude an alternative etiology.

[d] The presence of signs and symptoms consistent with sepsis syndrome indicates acute disseminated disease, whereas their absence denotes chronic disseminated disease.

[e] These tests are primarily applicable to aspergillosis and candidiasis and are not useful in diagnosing infections due to *Cryptococcus* species or Zygomycetes (e.g., *Rhizopus*, *Mucor*, or *Absidia* species). Detection of nucleic acid is not included, because there are as yet no validated or standardized methods.

**Table 3. Criteria for the diagnosis of endemic mycoses.**

| Diagnosis and criteria |
|---|
| Proven endemic mycosis |
| In a host with an illness consistent with an endemic mycosis, 1 of the following |
| Recovery in culture from a specimen obtained from the affected site or from blood |
| Histopathologic or direct microscopic demonstration of appropriate morphologic forms with a truly distinctive appearance characteristic of dimorphic fungi, such as *Coccidioides* species spherules, *Blastomyces dermatitidis* thick-walled broad-based budding yeasts, *Paracoccidioides brasiliensis* multiple budding yeast cells, and, in the case of histoplasmosis, the presence of characteristic intracellular yeast forms in a phagocyte in a peripheral blood smear or in tissue macrophages |
| For coccidioidomycosis, demonstration of coccidioidal antibody in CSF, or a 2-dilution rise measured in 2 consecutive blood samples tested concurrently in the setting of an ongoing infectious disease process |
| For paracoccidioidomycosis, demonstration in 2 consecutive serum samples of a precipitin band to paracoccidioidin concurrently in the setting of an ongoing infectious disease process |
| Probable endemic mycosis |
| Presence of a host factor, including but not limited to those specified in table 2, plus a clinical picture consistent with endemic mycosis and mycological evidence, such as a positive *Histoplasma* antigen test result from urine, blood, or CSF |

**NOTE.** Endemic mycoses includes histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, sporotrichosis, and infection due to *Penicillium marneffei*. Onset within 3 months after presentation defines a primary pulmonary infection. There is no category of possible endemic mycosis, as such, because neither host factors nor clinical features are sufficiently specific; such cases are considered to be of value too limited to include in clinical trials, epidemiological studies, or evaluations of diagnostic tests.

in our understanding of *Coccidioides* serological characteristics. Consequently, the presence of coccidioidal antibody in CSF was considered to be sufficient to fulfill the criteria for proven coccidioidomycosis. Similarly, the presence of capsular antigen in CSF was considered to be sufficiently distinctive to establish a diagnosis of disseminated cryptococcosis [25]. Urinary *Histoplasma* antigen supports a diagnosis of probable endemic mycosis, in conjunction with appropriate host and clinical criteria (table 3), but cannot be considered sufficient evidence of proven histoplasmosis, because *Histoplasma* antigen is also found in urine and serum of patients with coccidioidomycosis and blastomycosis [26].

***Probable IFD.*** Cases of probable IFD require that a host factor, clinical features, and mycological evidence be present, as outlined in tables 2 and 3.

***Possible IFD.*** The category of possible IFD was retained but was defined more strictly to include only those cases with the appropriate host factors and with sufficient clinical evidence consistent with IFD but for which there was no mycological support (table 2). However, this category was not considered appropriate for endemic mycosis, because host factors and clinical features are not sufficiently specific and because such cases would be of value too limited to include in clinical trials, epidemiological studies, or evaluations of diagnostic tests.

## COMMENTS

***Implications of the revised category of possible IFD.*** After enrollment into an interventional or diagnostic study, every effort should be made to upgrade the certainty of diagnosis for patients with possible IFD to the category of proven or probable IFD. These definitions may be applied at different times during the period of risk. For example, although a case might not meet the definition of possible, probable, or proven IFD at the beginning of a period of high risk, during which prophylaxis is given, the case may continue to evolve, such that the criteria may be met later.

The overrepresentation of dubious cases that resulted from the application of the original definitions made it imperative to redress the balance and to capture more patients with a higher probability of IFD while excluding patients who are unlikely to have invasive mycosis. Some members even argued that the category of possible IFD, as defined in the original set of definitions, should be abolished altogether. However, such a decision would reduce dramatically the number of candidates eligible for clinical studies of fungal pneumonia, making randomized trials nearly impossible to conduct. The corollary of retaining a better-defined category of possible IFD, to reduce the number of doubtful cases, was that greater emphasis was placed on mycological evidence for the categories of proven and probable IFD. This allows the category of possible IFD to be reserved for clinical manifestations fully consistent with fungal etiology but for which there is no mycological evidence available, although a reasonable attempt has been made to exclude an alternative etiology.

***Non–culture-based diagnostic tests.*** There was much discussion about indirect mycological tests, especially assays for detection of antigen and β-D-glucan. Since the first definitions were published [1], the FDA has approved the *Aspergillus* galactomannan EIA and, more recently, the assay for β-D-glucan, on the grounds that they were standardized, were validated, are available, and are fit to convey useful information [8, 19, 27]. However, controversy arose about the interpretation of the index for the galactomannan assay, which was originally set at 1.5 and was applied in Europe but which was lowered to 0.5

after review by the FDA. This cutoff value has been shown recently to improve the overall performance of the test for adult hematology patients [28]. Because the issue remains contentious, the decision was made to place the onus on the manufacturers of commercial tests and to adopt whatever threshold values they recommend.

We had hoped that nucleic acid–detection tests, such as PCR, would have improved enough to incorporate the results of these tests into the definitions. However, standardization and validation have not yet been attained for these platforms.

***Limitations of the revised definitions.*** The revised definitions apply to immunocompromised patients but not necessarily to critically ill patients in the intensive care unit who, nonetheless, may develop possible or probable IFD [29]. The group recognized this as an omission but was unable to find a sufficient basis for identifying the appropriate host factors, even though there may be mycological evidence, such as recovery of *Aspergillus* species from bronchial secretions or a positive $\beta$-D-glucan test result. The group, therefore, concluded that the body of evidence supporting a diagnosis other than proven IFD is not sufficiently mature at present.

The definitions are not a substitute for complete clinicopathologic descriptions and classifications of IFD, as have been published recently for aspergillosis [21]. The failure to meet the criteria for IFD does not mean that there is no IFD, only that there is insufficient evidence to support the diagnosis. This is the most compelling reason for not employing these definitions in daily clinical practice.

We anticipate that the field of diagnosis will continue to evolve, so that there will come a time when the definitions may be formally evaluated for their sensitivity and specificity. Until then, additional revisions of the present set of definitions are likely, but they should be contemplated carefully. The words and phrases chosen here were selected on the basis of extensive debate and discussion. Seemingly, slight changes may have unexpectedly profound consequences in the design, implementation, and interpretation of clinical trials.

These revised definitions of IFD categories are intended to advance clinical and epidemiological research and, as such, may serve as a useful model for defining other infections in high-risk patients. The definitions are not meant to be used to guide clinical practice but must be applied consistently if they are to continue to achieve their primary goal of fostering communication, furthering our understanding of the epidemiology and evolution of IFD, and facilitating our ability to test the efficacy of therapeutic regimens and strategies.

## AUTHOR AFFILIATIONS

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T.C. has received grant support from Bio-Rad Laboratories, Essex Pharma, Merck, Roche Diagnostics, and Wako; has been an advisor/consultant for Essex Pharma, Merck Sharp & Dohme, Novartis, and Pfizer; and has been on the speakers' bureau for Merck Sharp & Dohme and Pfizer. P.G.P. has received grant support from Astellas Pharma, Merck, Pfizer, and Schering-Plough; has been an advisor/consultant for Astellas Pharma, Merck, Pfizer, and Schering-Plough; and has been on the speakers' bureau for Astellas Pharma, Merck, Pfizer, and Schering-Plough. J.M. has received grant support from Bio-Rad Laboratories, Merck Sharp & Dohme, and Schering-Plough; has been an advisor/consultant for Bio-Rad Laboratories, Fujisawa Healthcare, Gilead Sciences, Merck Sharp & Dohme, Nektar Therapeutics, Pfizer, Schering-Plough, and Zeneus (now Cephalon); and has been on the speakers' bureau for Bio-Rad Laboratories, Fujisawa Healthcare, Gilead Sciences, Merck Sharp & Dohme, Pfizer, Schering-Plough, and Zeneus (now Cephalon). O.L. has received grant support from Gilead Sciences, Merck Sharp & Dohme, and Pfizer and has been on the speakers' bureau for Astellas Pharma, Gilead Sciences, Merck Sharp & Dohme, Pfizer, and Schering-Plough. C.A.K. has received grant support from Astellas Pharma, Merck, and Schering-Plough and has been on the speakers' bureau for Astellas Pharma, Merck, Pfizer, and Schering-Plough. D.W.D. has received grant support from Astellas Pharma, Basilea Pharmaceutica, the Chronic Granulomatous Disease Research Trust, the European Union, F2G, the Fungal Research Trust, Indevus Pharmaceuticals, the Medical Research Council, Merck Sharp & Dohme, the Moulton Trust, the National Institute of Allergy and Infectious Diseases, Ortho-Biotech, Pfizer, and the Wellcome Trust; has been an advisor/consultant for Astellas Pharma, Basilea Pharmaceutica, Daiichi Sankyo, F2G, Gilead Sciences, Indevus Pharmaceuticals, Nektar Therapeutics, Pfizer, Schering-Plough, Sigma Tau, Vicuron (now Pfizer), and York Pharma; has been on the speakers' bureau for Astellas Pharma, Astra-Zeneca, Chiron, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer, and Schering-Plough; and holds founder shares of F2G and Myconostica. T.F.P. has received grant support from Astellas Pharma, Enzon, Merck, Nektar Therapeutics, Pfizer, and Schering-Plough; has been an advisor/consultant for Basilea Pharmaceutica, Merck, Nektar Therapeutics, Pfizer, Schering-Plough, and Stiefel Laboratories; and has been on the speakers' bureau for Merck and Pfizer. G.M. has been an advisor/consultant for Gilead Sciences, Merck Sharp & Dohme, Pfizer, and Sanofi-Aventis; has been on the speakers' bureau for Amgen, Cephalon, Gilead Sciences, Merck Sharp & Dohme, Ortho-Biotech, and Pfizer; and has received travel grants from Amgen, Merck Sharp & Dohme, Novartis, Pfizer, and Roche. R.H. has received grant support from Pfizer; has been an advisor/consultant for Astellas Pharma, Gilead Sciences, Merck, Novartis, Pfizer, and Schering-Plough; and has been on the speakers' bureau for Gilead Sciences, Pfizer, and Schering-Plough. W.W.H. has received grant support from Astellas Pharma, Gilead Sciences, and Schering-Plough and has been an advisor/consultant for Pfizer. C.C.K. has received grant support from Gilead Sciences, Merck, and Pfizer and has been an advisor/consultant for Astellas Pharma, Gilead Sciences, ICN (now Valeant), Janssen, Merck, Pfizer, and Schering-Plough. B.J.K. has been an advisor/consultant for Basilea Pharmaceutica, F2G, Novartis, Pfizer, and Schering-Plough and has been on the speakers' bureau for Pfizer and Schering-Plough. K.A.M. has been an advisor/consultant for Astellas Pharma, Basilea Pharmaceutica, Enzon, Merck, Pfizer, and Schering-Plough. F.C.O. has received grant support from Merck and Sharp & Dohme; has been an advisor/consultant for Astellas Pharma, Italfarmaco, Merck Sharp & Dohme, Pfizer, Schering-Plough, and Syngenta; has been on the speakers' bureau for Astellas Pharma, Merck Sharp & Dohme, Pfizer, and Schering-Plough; and holds shares of Johnson & Johnson. J.R.P. has received grant support from Astellas Pharma, Enzon, Merck, Pfizer, and Schering-Plough; has been an advisor/consultant for Astellas Pharma, Enzon, Merck, Pfizer, and Schering-Plough; and has been on the speakers' bureau for Astellas Pharma, Enzon, Merck, Pfizer, and Schering-Plough. M.R. has received grant support from Merck Sharp & Dohme and Pfizer; has been an advisor/consultant for Basilea Pharmaceutica, Essex Pharma, Gilead Sciences, Merck Sharp & Dohme, Novartis, and Pfizer; and has been on the speakers' bureau for Essex Pharma, Gilead Sciences, Merck Sharp & Dohme, Novartis, and Pfizer. B.H.S. has received grant support from Pfizer; has been an advisor/consultant for Berlex Laboratories, Pfizer, and Schering-Plough; and has been on the speakers' bureau for Merck and Pfizer. J.D.S. has received grant support from Merck, the National Institutes of Health, and Pfizer; has been an advisor/consultant for Merck and Pfizer; and has been on the speakers' bureau for Merck, Pfizer, and Schering-Plough. T.C.S. has received grant support from Gilead Sciences, Merck Sharp & Dohme, and Pfizer and has been an advisor/consultant for Gilead Sciences, Merck Sharp & Dohme, Pfizer, and Schering-Plough. C.V. has been an advisor/consultant for Gilead Sciences, Novartis, and Schering-Plough and has been on the speakers' bureau for Gilead Sciences, Merck Sharp & Dohme, Pfizer, Schering-Plough, and Wyeth Pharmaceuticals. J.R.W. has received grant support from Merck and Pfizer; has been an advisor/consultant for Basilea Pharmaceutica, Merck, Nektar Therapeutics, and Pfizer; and has been on the speakers' bureau for Merck and Pfizer. T.Z. has received grant support from Merck. All other authors: no conflicts.

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## 12.9 ECOG Performance Status

| ECOG PERFORMANCE STATUS* | |
|---|---|
| **Grade** | **ECOG** |
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair |
| 5 | Dead |

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

## 12.10 Product Circular of Posaconazole Oral Suspension

Approved date: Jun.3, 2013

Modified date: July 18, 2013; Oct 18, 2014; Feb 3, 2015; Jun 9, 2017

# Product Circular of Posaconazole Oral Suspension

Please read this leaflet carefully before you start to take this medicine.

**[Name]**

Generic Name: Posaconazole Oral Suspension

Brand Name: Noxafil®

English Name: Posaconazole Oral Suspension

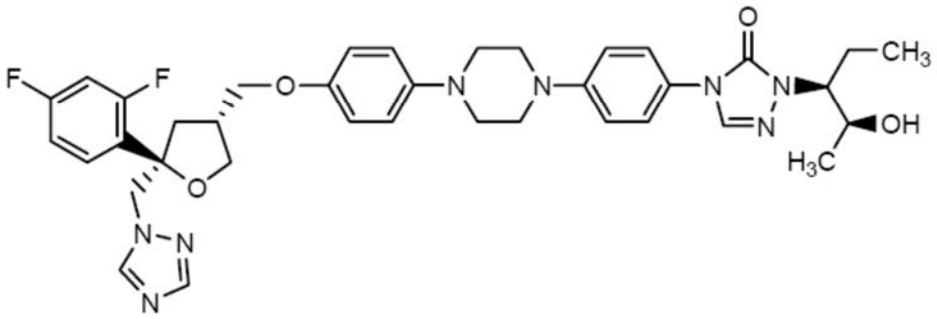
Chinese Pin Yin: Boshakangzuo Koufuhunxuanye

**[Composition]**

Active Ingredient: Posaconazole

Chemical Name: 4-[4-[4-[4-[[(3R,5R)-5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1S,2S)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4- triazol-3-one

Chemical Structure:



Empirical formula: $C_{37}H_{42}F_2N_8O_4$

Molecular weight: 700.8.

Excipients**:** artificial cherry flavor purified water, citric acid monohydrate, glycerol, liquid glucose, polysorbate 80, simeticone, sodium benzoate (E211), sodium citrate dehydrate, titanium dioxide (E171), xanthan gum

**[Description]**

A white suspension; translucent to opaque white semi-solid particles may be observed.

**[Indications]**

1. Prophylaxis of Invasive Aspergillus and Candida Infections

NOXAFIL® Oral Suspension is indicated for prophylaxis of invasive Aspergillus and Candida infections in patients, 13 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graftversus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

2. Treatment of Oropharyngeal Candidiasis Including Oropharyngeal Candidiasis Refractory to Itraconazole and/or Fluconazole

NOXAFIL is indicated for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole.

**[Strength]**

Each ml of oral suspension contains 40 mg of posaconazole.

**[Dosage & Administration]**

**1. Dosage**

**Table 1**

| Indication | Dose and Duration of Therapy |
|---|---|
| Prophylaxis of Invasive Fungal Infections | 200 mg (5 mL) three times a day. The duration of therapy is based on recovery from neutropenia or immunosuppression. |
| Oropharyngeal Candidiasis | Loading dose of 100 mg (2.5 mL) twice a day on the first day, then 100 mg (2.5 mL) once a day for 13 days. |
| Oropharyngeal Candidiasis Refractory to itraconazole and/or fluconazole | 400 mg (10 mL) twice a day. Duration of therapy should be based on the severity of the patient's underlying disease and clinical response. |

**2. Administration Instructions**

NOXAFIL Oral Suspension is available in 4-ounce (123 mL) amber glass bottles with child-resistant closures (NDC 0085-1328-01) containing 105 mL of suspension (40 mg of posaconazole per mL).

Shake NOXAFIL Oral Suspension well before use.

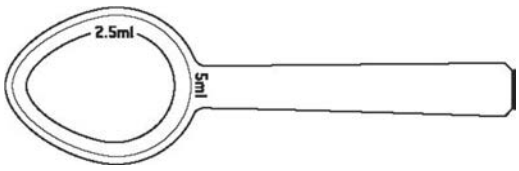



Figure 1: A measured dosing spoon is provided, marked for doses of 2.5 mL and 5 mL.

It is recommended that the spoon is rinsed with water after each administration and before storage.

Each dose of NOXAFIL should be administered with a full meal or with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale) in patients who cannot eat a full meal.

To enhance the oral absorption of posaconazole and optimize plasma concentrations:

1) Each dose of NOXAFIL should be administered during or immediately (i.e., within 20 minutes) following a full meal. In patients who cannot eat a full meal, each dose of NOXAFIL should be administered with a liquid nutritional supplement or an acidic carbonated beverage. For patients who cannot eat a full meal or tolerate an oral nutritional supplement or an acidic carbonated beverage, alternative antifungal therapy should be considered or patients should be monitored closely for breakthrough fungal infections.
2) Patients who have severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections.
3) Coadministration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections.

**3. Renal Insufficiency**

Following single-dose administration of 400 mg of the oral suspension, there was no significant effect of mild (CLcr: 50-80 mL/min/1.73 $m^2$, n=6) and moderate (CLcr: 20-49 mL/min/1.73 $m^2$, n=6) renal insufficiency on posaconazole pharmacokinetics; therefore, no dose adjustment is required in patients with mild to moderate renal impairment. In subjects with severe renal insufficiency (CLcr: < 20 mL/min/1.73 $m^2$), the mean plasma exposure (AUC) was similar to that in patients with normal renal function (CLcr: >80 mL/min/1.73 $m^2$); however, the range of the AUC estimates was highly variable (CV=96%) in these subjects with severe renal insufficiency as compared to that in the other renal impairment groups (CV< 40%). Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections.

**4. Hepatic Insufficiency**

After a single oral dose of posaconazole 400 mg, the mean AUC was 43%, 27%, and 21% higher in subjects with mild (Child-Pugh Class A, N=6), moderate (Child-Pugh Class B, N=6), and severe (Child-Pugh Class C, N=6) hepatic insufficiency, respectively, compared to subjects with normal hepatic function (N=18). Compared to subjects with normal hepatic function, the mean $C_{max}$ was 1% higher, 40% higher, and 34% lower in subjects with mild, moderate, and severe hepatic insufficiency, respectively. The mean apparent oral clearance (CL/F) was reduced by 18%, 36%, and 28% in subjects with mild, moderate, and severe hepatic insufficiency, respectively, compared to subjects with normal hepatic function. The elimination half-life ($t_{½}$) was 27 hours, 39 hours, 27 hours, and 43 hours in subjects with normal hepatic function and mild, moderate, and severe hepatic insufficiency, respectively.

It is recommended that no dose adjustment of NOXAFIL is needed in patients with mild to severe hepatic insufficiency (Child-Pugh Class A, B, and C) [see Precautions].

**5. Gender**

The pharmacokinetics of posaconazole are comparable in men and women. No adjustment in the dosage of NOXAFIL is necessary based on gender.

**6. Race**

The pharmacokinetic profile of posaconazole is not significantly affected by race. No adjustment in the dosage of NOXAFIL is necessary based on race.

**[Side Effects]**

**1. Serious and Other Important Adverse Reactions**

The following serious and otherwise important adverse reactions are discussed in detail in another section of the labeling:

1) Hypersensitivity

2) Arrhythmias and QT Prolongation

3) Hepatic Toxicity

**2. Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of NOXAFIL cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of posaconazole therapy has been assessed in 1844 patients in clinical trials. This includes 605 patients in the active-controlled prophylaxis studies, 557 patients in the active-controlled OPC studies, 239 patients in refractory OPC studies, and 443 patients from other indications. This represents a heterogeneous population, including immunocompromised patients, e.g., patients with hematological malignancy, neutropenia post-chemotherapy, graft vs. host disease post hematopoietic stem cell transplant, and HIV infection, as well as non-neutropenic patients. This patient population was 71% male, had a mean age of 42 years (range 8-84 years, 6% of patients were ≥65 years of age and 1% was <18 years of age), and were 64% white, 16% Hispanic, and 36% non-white (including 14% black). Posaconazole therapy was given to 171 patients for ≥6 months, with 58 patients receiving posaconazole therapy for ≥12 months. Table 2 presents treatment-emergent adverse reactions observed at an incidence of >10% in posaconazole prophylaxis studies. Table 3 presents treatment-emergent adverse reactions observed at an incidence of at least 10% in the OPC/rOPC studies.

**Prophylaxis of Aspergillus and Candida:**

In the 2 randomized, comparative prophylaxis studies, the safety of posaconazole 200 mg three times a day was compared to fluconazole 400 mg once daily or itraconazole 200 mg twice a day in severely immunocompromised patients.

The most frequently reported adverse reactions (>30%) in the prophylaxis clinical trials were fever, diarrhea and nausea.

The most common adverse reactions leading to discontinuation of posaconazole in the prophylaxis studies were associated with GI disorders, specifically, nausea (2%), vomiting (2%), and hepatic enzymes increased (2%).

TABLE 2: Study 1 and Study 2. Number (%) of Randomized Subjects Reporting Treatment-Emergent Adverse Reactions: Frequency of at Least 10% in the Posaconazole or Fluconazole Treatment Groups (Pooled Prophylaxis Safety Analysis)

| Body System Preferred Term | Posaconazole (n=605) | Fluconazole (n=539) | Itraconazole (n=58) |
|---|---|---|---|
| Subjects Reporting any Adverse Reaction | 595 (98) | 531 (99) | 58 (100) |
| Body as a Whole - General Disorders | | | |
| Fever | 274 (45) | 254 (47) | 32 (55) |
| Headache | 171 (28) | 141 (26) | 23 (40) |
| Rigors | 122 (20) | 87 (16) | 17 (29) |
| Fatigue | 101 (17) | 98 (18) | 5 (9) |
| Edema Legs | 93 (15) | 67 (12) | 11 (19) |
| Anorexia | 92 (15) | 94 (17) | 16 (28) |
| Dizziness | 64 (11) | 56 (10) | 5 (9) |
| Edema | 54 (9) | 68 (13) | 8 (14) |
| Weakness | 51 (8) | 52 (10) | 2 (3) |
| Cardiovascular Disorders, General | | | |
| Hypertension | 106 (18) | 88 (16) | 3 (5) |
| Hypotension | 83 (14) | 79 (15) | 10 (17) |
| Disorders of Blood and Lymphatic System | | | |
| Anemia | 149 (25) | 124 (23) | 16 (28) |
| Neutropenia | 141 (23) | 122 (23) | 23 (40) |
| Febrile Neutropenia | 118 (20) | 85 (16) | 23 (40) |
| Disorders of the Reproductive System and Breast | | | |
| Vaginal Hemorrhage* | 24 (10) | 20 (9) | 3 (12) |
| Gastrointestinal System Disorders | | | |
| Diarrhea | 256 (42) | 212 (39) | 35 (60) |
| Nausea | 232 (38) | 198 (37) | 30 (52) |
| Vomiting | 174 (29) | 173 (32) | 24 (41) |
| Abdominal Pain | 161 (27) | 147 (27) | 21 (36) |
| Constipation | 126 (21) | 94 (17) | 10 (17) |
| Mucositis NOS | 105 (17) | 68 (13) | 15 (26) |
| Dyspepsia | 61 (10) | 50 (9) | 6 (10) |
| Heart Rate and Rhythm Disorders | | | |
| Tachycardia | 72 (12) | 75 (14) | 3 (5) |
| Infection and Infestations | | | |
| Bacteremia | 107 (18) | 98 (18) | 16 (28) |
| Herpes Simplex | 88 (15) | 61 (11) | 10 (17) |
| Cytomegalovirus Infection | 82 (14) | 69 (13) | 0 |
| Pharyngitis | 71 (12) | 60 (11) | 12 (21) |
| Upper Respiratory Tract Infection | 44 (7) | 54 (10) | 5 (9) |
| Liver and Biliary System Disorders | | | |
| Bilirubinemia | 59 (10) | 51 (9) | 11 (19) |
| Metabolic and Nutritional Disorders | | | |
| Hypokalemia | 181 (30) | 142 (26) | 30 (52) |
| Hypomagnesemia | 110 (18) | 84 (16) | 11 (19) |
| Hyperglycemia | 68 (11) | 76 (14) | 2 (3) |
| Hypocalcemia | 56 (9) | 55 (10) | 5 (9) |
| Musculoskeletal System Disorders | | | |
| Musculoskeletal Pain | 95 (16) | 82 (15) | 9 (16) |
| Arthralgia | 69 (11) | 67 (12) | 5 (9) |
| Back Pain | 63 (10) | 66 (12) | 4 (7) |
| Platelet, Bleeding and Clotting Disorders | | | |
| Thrombocytopenia | 175 (29) | 146 (27) | 20 (34) |

| Body System Preferred Term | Posaconazole (n=605) | Fluconazole (n=539) | Itraconazole (n=58) |
|---|---|---|---|
| Petechiae | 64 (11) | 54 (10) | 9 (16) |
| Psychiatric Disorders | | | |
| Insomnia | 103 (17) | 92 (17) | 11 (19) |
| Anxiety | 52 (9) | 61 (11) | 9 (16) |
| Respiratory System Disorders | | | |
| Coughing | 146 (24) | 130 (24) | 14 (24) |
| Dyspnea | 121 (20) | 116 (22) | 15 (26) |
| Epistaxis | 82 (14) | 73 (14) | 12 (21) |
| Skin and Subcutaneous Tissue Disorders | | | |
| Rash | 113 (19) | 96 (18) | 25 (43) |
| Pruritus | 69 (11) | 62 (12) | 11 (19) |
| * Percentages of sex-specific adverse reactions are based on the number of males/females. NOS = not otherwise specified. | | | |

**HIV Infected Subjects with OPC:**

In 2 randomized comparative studies in OPC, the safety of posaconazole at a dose of ≤ 400 mg QD in 557 HIV-infected patients was compared to the safety of fluconazole in 262 HIV-infected patients at a dose of 100 mg QD.

An additional 239 HIV-infected patients with refractory OPC received posaconazole in 2 non-comparative trials for refractory OPC (rOPC). Of these subjects, 149 received the 800-mg/day dose and the remainder received the ≤400-mg QD dose.

In the OPC/rOPC studies, the most common adverse reactions were fever, diarrhea, nausea, headache, and vomiting.

The most common adverse reactions that led to treatment discontinuation of posaconazole in the Controlled OPC Pool included respiratory insufficiency (1%) and pneumonia (1%). In the refractory OPC pool, the most common adverse reactions that led to treatment discontinuation of posaconazole were AIDS (7%) and respiratory insufficiency (3%).

TABLE 3: Treatment-Emergent Adverse Reactions with Frequency of at Least 10% in OPC Studies (Treated Population)

| | Number (%) of Subjects | | |
|---|---|---|---|
| | Controlled OPC Pool | | Refractory OPC Pool |
| | Posaconazole | Fluconazole | Posaconazole |
| Body System Preferred Term | n=557 | n=262 | n=239 |
| Subjects Reporting any Adverse Reaction* | 356 (64) | 175 (67) | 221 (92) |
| Body as a Whole – General Disorders | | | |
| Fever | 34 (6) | 22 (8) | 82 (34) |
| Headache | 44 (8) | 23 (9) | 47 (20) |
| Anorexia | 10 (2) | 4 (2) | 46 (19) |
| Fatigue | 18 (3) | 12 (5) | 31 (13) |
| Asthenia | 9 (2) | 5 (2) | 31 (13) |
| Rigors | 2 (<1) | 4 (2) | 29 (12) |
| Pain | 4 (1) | 2 (1) | 27 (11) |
| Disorders of Blood and Lymphatic System | | | |
| Neutropenia | 21 (4) | 8 (3) | 39 (16) |
| Anemia | 11 (2) | 5 (2) | 34 (14) |
| Gastrointestinal System Disorders | | | |
| Diarrhea | 58 (10) | 34 (13) | 70 (29) |
| Nausea | 48 (9) | 30 (11) | 70 (29) |
| Vomiting | 37 (7) | 18 (7) | 67 (28) |
| Abdominal Pain | 27 (5) | 17 (6) | 43 (18) |
| Infection and Infestations | | | |
| Candidiasis, Oral | 3 (1) | 1 (<1) | 28 (12) |
| Herpes Simplex | 16 (3) | 8 (3) | 26 (11) |
| Pneumonia | 17 (3) | 6 (2) | 25 (10) |
| Metabolic and Nutritional Disorders | | | |
| Weight Decrease | 4 (1) | 2 (1) | 33 (14) |
| Dehydration | 4 (1) | 7 (3) | 27 (11) |
| Psychiatric Disorders | | | |
| Insomnia | 8 (1) | 3 (1) | 39 (16) |
| Respiratory System Disorders | | | |
| Coughing | 18 (3) | 11 (4) | 60 (25) |
| Dyspnea | 8 (1) | 8 (3) | 28 (12) |
| Skin and Subcutaneous Tissue Disorders | | | |
| Rash | 15 (3) | 10 (4) | 36 (15) |
| Sweating Increased | 13 (2) | 5 (2) | 23 (10) |

OPC=oropharyngeal candidiasis; SGOT=serum glutamic oxaloacetic transaminase (same as AST); SGPT=serum glutamic pyruvic transaminase (same as ALT).
* Number of subjects reporting treatment-emergent adverse reactions at least once during the study, without regard to relationship to treatment. Subjects may have reported more than 1 event.

Adverse reactions were reported more frequently in the pool of patients with refractory OPC. Among these highly immunocompromised patients with advanced HIV disease, serious adverse reactions (SARs) were reported in 55% (132/239). The most commonly reported SARs were fever (13%) and neutropenia (10%).

**Less Common Adverse Reactions:**

- **Blood and lymphatic system disorders:** hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, neutropenia aggravated
- **Endocrine disorders:** adrenal insufficiency
- **Nervous system disorders:** paresthesia
- **Immune system disorders:** allergic reaction
- **Cardiac disorders:** Torsades depointes
- **Vascular disorders:** pulmonary embolism
- **Liver and Biliary System Disorders:** bilirubinemia, hepatic enzymes increased, hepatic function abnormal, hepatitis, hepatomegaly, jaundice, SGOT Increased, SGPT Increased
- **Metabolic and Nutritional Disorders:** hypokalemia
- **Platelet, Bleeding, and Clotting Disorders:** thrombocytopenia
- **Renal & Urinary System Disorders:** renal failure acute

**Clinical Laboratory Values:**

In healthy volunteers and patients, elevation of liver function test values did not appear to be associated with higher plasma concentrations of posaconazole. The majorities of abnormal liver function tests were minor, transient, and did not lead to discontinuation of therapy.

For the prophylaxis studies, the number of patients with changes in liver function tests from Common Toxicity Criteria (CTC) Grade 0, 1, or 2 at baseline to Grade 3 or 4 during the study is presented in Table 4.

TABLE 4: Study 1 and Study 2. Changes in Liver Function test results from CTC Grade 0, 1 or 2 at Baseline to Grade 3 or 4

| Number (%) of Patients With Change* | | |
|---|---|---|
| **Study 1** | | |
| Laboratory Parameter | Posaconazole n=301 | Fluconazole n=299 |
| AST | 11/266 (4) | 13/266 (5) |
| ALT | 47/271 (17) | 39/272 (14) |
| Bilirubin | 24/271 (9) | 20/275 (7) |
| Alkaline Phosphatase | 9/271 (3) | 8/271 (3) |
| **Study 2** | | |
| Laboratory Parameter | Posaconazole (n=304) | Fluconazole/Itraconazole (n=298) |
| AST | 9/286 (3) | 5/280 (2) |
| ALT | 18/289 (6) | 13/284 (5) |
| Bilirubin | 20/290 (7) | 25/285 (9) |
| Alkaline Phosphatase | 4/281 (1) | 1/276 (<1) |
| *Change from Grade 0 to 2 at baseline to Grade 3 or 4 during the study. These data are presented in the form X/Y, where X represents the number of patients who met the criterion as indicated, and Y represents the number of patients who had a baseline observation and at least one post-baseline observation.<br>CTC = Common Toxicity Criteria; AST= Aspartate Aminotransferase; ALT= Alanine Aminotransferase. | | |

The number of patients treated for OPC with clinically significant liver function test (LFT) abnormalities at any time during the studies is provided in Table 5. (LFT abnormalities were present in some of these patients prior to initiation of the study drug).

TABLE 5: Clinically Significant Laboratory Test Abnormalities without Regard to Baseline Value

| | Controlled | | Refractory |
|---|---|---|---|
| | Posaconazole | Fluconazole | Posaconazole |
| **Laboratory Test** | **n=557(%)** | **n=262(%)** | **n=239(%)** |
| ALT > 3.0 x ULN | 16/537 (3) | 13/254 (5) | 25/226 (11) |
| AST > 3.0 x ULN | 33/537 (6) | 26/254 (10) | 39/223 (17) |
| Total Bilirubin > 1.5 x ULN | 15/536 (3) | 5/254 (2) | 9/197 (5) |
| Alkaline Phosphatase > 3.0 x ULN | 17/535 (3) | 15/253 (6) | 24/190 (13) |
| ALT= Alanine Aminotransferase; AST= Aspartate Aminotransferase. | | | |

**3. Postmarketing Experience**

No clinically significant postmarketing adverse reactions were identified that have not previously **been reported** during clinical trials experience.

**[Contraindications]**

**1. Hypersensitivity**

NOXAFIL is contraindicated in persons with known hypersensitivity to posaconazole, any component of NOXAFIL, or other azole antifungal agents.

**2. Use with Sirolimus**

NOXAFIL is contraindicated with sirolimus. Concomitant administration of NOXAFIL with sirolimus increases the sirolimus blood concentrations by approximately 9 fold and can result in sirolimus toxicity.

**3. QT Prolongation with Concomitant Use with CYP3A4 Substrates**

NOXAFIL is contraindicated with CYP3A4 substrates that prolong the QT interval. Concomitant administration of NOXAFIL with the CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide and quinidine may result in increased plasma concentrations of these drugs, leading to QTc prolongation and rare occurrences of torsades de pointes.

**4. HMG-CoA Reductase Inhibitors Primarily Metabolized Through CYP3A4**

Coadministration with the HMG-CoA reductase inhibitors that are primarily metabolized through CYP3A4 (e.g., atorvastatin, lovastatin, and simvastatin) is contraindicated since increased plasma concentration of these drugs can lead to rhabdomyolysis.

**5. Use with Ergot Alkaloids**

Posaconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism. Coadministration of posaconazole and ergot alkaloids is contraindicated.

**[Precaution]**

**1．Calcineurin-Inhibitor Drug Interactions**

Concomitant administration of NOXAFIL with cyclosporine or tacrolimus increases the whole blood trough concentrations of these calcineurin-inhibitors. Nephrotoxicity and leukoencephalopathy (including isolated deaths) have been reported in clinical efficacy studies in patients with elevated cyclosporine concentrations. Frequent monitoring of tacrolimus or cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus or cyclosporine dose adjusted accordingly.

**2．Arrhythmias and QT Prolongation**

Some azoles, including posaconazole, have been associated with prolongation of the QT interval on the electrocardiogram. In addition, rare cases of torsades de pointes have been reported in patients taking posaconazole.

Results from a multiple time-matched ECG analysis in healthy volunteers did not show any increase in the mean of the QTc interval. Multiple, time-matched ECGs collected over a 12-hour period were recorded at baseline and steady-state from 173 healthy male and female volunteers (18-85 years of age) administered posaconazole 400 mg BID with a high-fat meal. In this pooled analysis, the mean QTc (Fridericia) interval change from baseline was –5 msec following administration of the recommended clinical dose. A decrease in the QTc(F) interval (–3 msec) was also observed in a small number of subjects (n=16) administered placebo. The placebo-adjusted mean maximum QTc(F) interval change from baseline was < 0msec (–8msec). No healthy subject administered posaconazole had a QTc(F) interval ≥500 msec or an increase ≥60 msec in their QTc(F) interval from baseline.

Noxafil must not be administered with medicinal products that are substrates for CYP3A4 and are known to prolong the QTc interval.

Noxafil should be administered with caution to patients who probably with drug related arrhythmic.

Noxafil must be administered with caution to patients with pro-arrhythmic conditions such as:

- Congenital or acquired QTc prolongation
- Cardiomyopathy, especially in the presence of cardiac failure
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant use with medicinal products known to prolong the QTc interval (other than those mentioned in Contraindications).

Electrolyte disturbances, especially those involving potassium, magnesium or calcium levels, should be monitored and corrected as necessary before and during posaconazole therapy.

Posaconazole is an inhibitor of CYP3A4 and should only be used under specific circumstances during treatment with other medicinal products that are metabolised by CYP3A4 (see in Drug interactions).

**3. Hepatic Toxicity**

Hepatic reactions (e.g., mild to moderate elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and/or clinical hepatitis) have been reported in clinical trials. The elevations in liver function tests were generally reversible on discontinuation of therapy, and in some instances these tests normalized without drug interruption and rarely required drug discontinuation. Isolated cases of more severe hepatic reactions including cholestasis or hepatic failure including deaths have been reported in patients with serious underlying

medical conditions (e.g., hematologic malignancy) during treatment with posaconazole. These severe hepatic reactions were seen primarily in subjects receiving the 800 mg daily (400 mg BID or 200 mg QID) in clinical trials.

Liver function tests should be evaluated at the start of and during the course of posaconazole therapy. Patients who develop abnormal liver function tests during posaconazole therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of posaconazole must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to posaconazole.

**4. Use with Midazolam**

Concomitant administration of NOXAFIL with midazolam increases the midazolam plasma concentrations by approximately 5 fold. Increased plasma midazolam concentrations could potentiate and prolong hypnotic and sedative effects. Patients must be monitored closely for adverse effects associated with high plasma concentrations of midazolam and benzodiazepine receptor antagonists must be available to reverse these effects.

**5. Others**

**Hypersensitivity**

There is no information regarding cross-sensitivity between posaconazole and other azole antifungal agents. Caution should be used when prescribing Noxafil to patients with hypersensitivity to other azoles.

**Gastrointestinal dysfunction**

There are limited pharmacokinetic data in patients with severe gastrointestinal dysfunction (such as severe diarrhoea). Patients who have severe diarrhoea or vomiting should be monitored closely for breakthrough fungal infections.

**Rifamycin antibacterials (rifampicin, rifabutin), certain anticonvulsants (phenytoin, carbamazepine, phenobarbital, primidone), efavirenz and cimetidine**

Posaconazole concentrations may be significantly lowered in combination; therefore, concomitant use with posaconazole should be avoided unless the benefit to the patient outweighs the risk.

**Excipients**

This medicinal product contains approximately 1.75 g of glucose per 5 ml of suspension. Patients with glucose-galactose malabsorption should not take this medicine.

**Effects on ability to drive and use machines**

No studies on the effects of posaconazole on the ability to drive and use machines have been performed. Since certain adverse reactions (e.g. dizziness, somnolence, etc.) have been reported with posaconazole use, which potentially may affect driving/operating machinery, caution needs to be used.

**[Pregnancy & Nursing Mothers]**

**Pregnancy Category C:**

There are no adequate and well-controlled studies in pregnant women. NOXAFIL should be used in pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Posaconazole has been shown to cause skeletal malformations (cranial malformations and missing ribs) in rats when given in doses ≥27 mg/kg (≥1.4 times the 400-mg BID regimen based on steady-

state plasma concentrations of drug in healthy volunteers). The no-effect dose for malformations in rats was 9 mg/kg, which is 0.7 times the exposure achieved with the 400-mg BID regimen. No malformations were seen in rabbits at doses up to 80 mg/kg. In the rabbit, the no-effect dose was 20 mg/kg, while high doses of 40 mg/kg and 80 mg/kg, 2.9 or 5.2 times the exposure achieved with the 400-mg BID regimen, caused an increase in resorptions. In rabbits dosed at 80 mg/kg, a reduction in body weight gain of females and a reduction in litter size were seen.

**Nursing Mothers**

Posaconazole is excreted in milk of lactating rats. It is not known whether NOXAFIL is excreted in human milk. Because of the potential for serious adverse reactions from NOXAFIL in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Fertility**

Posaconazole had no effect on fertility of male rats at a dose up to 180 mg/kg (1.7 times the 400-mg BID regimen based on steady-state plasma concentrations in healthy volunteers) or female rats at a dose up to 45 mg/kg (2.2 times the 400-mg BID regimen). There is no clinical experience assessing the impact of posaconazole on fertility in humans.

**[Pediatric Use]**

The safety and effectiveness of posaconazole have been established in the age groups 13 to 17 years of age. The safety and effectiveness of posaconazole in pediatric patients below the age of 13 years have not been established. Use of posaconazole in these age groups is supported by evidence from adequate and well-controlled studies of posaconazole in adults with additional data.

A total of 12 patients 13 to 17 years of age received 600 mg/day (200 mg three times a day) for prophylaxis of invasive fungal infections. The safety profile in these patients <18 years of age appears similar to the safety profile observed in adults. Based on pharmacokinetic data in 10 of these pediatric patients, the mean steady-state average posaconazole concentration (Cav) was similar between these patients and adults (≥18 years of age).

A total of 16 patients 8 to 17 years of age were treated with 800 mg/day (400 mg twice a day or 200 mg four times a day) in a study for another indication. Based on pharmacokinetic data in 12 of these pediatric patients, the mean steady-state average posaconazole concentration (Cav) was similar between these patients and adults (≥18 years of age).

In the prophylaxis studies, the mean steady-state posaconazole average concentration (Cav) was similar among ten adolescents (13 to 17 years of age) and adults (≥18 years of age). This is consistent with pharmacokinetic data from another study in which mean steady-state posaconazole Cav from 12 adolescent patients (8-17 years of age) was similar to that in the adults (≥18 years of age).

**[Use In the Elderly]**

Of the 605 patients randomized to posaconazole in the prophylaxis clinical trials, 63 (10%) were ≥65 years of age. In addition, 48 patients treated with ≥800-mg/day posaconazole in another indication were ≥65 years of age. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

The pharmacokinetics of posaconazole are comparable in young and elderly subjects (≥65 years of age). No adjustment in the dosage of NOXAFIL is necessary in elderly patients (≥65 years of age) based on age.

No overall differences in the pharmacokinetics and safety were observed between elderly and young subjects during clinical trials, but greater sensitivity of some older individuals cannot be ruled out.

**[Drug Interactions]**

Posaconazole is primarily metabolized via UDP glucuronidation and is a substrate of p-glycoprotein efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. Posaconazole is also a strong inhibitor of CYP3A4. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole.

**1. Immunosuppressants Metabolized by CYP3A4**

Sirolimus: Repeat dose administration of oral posaconazole (400 mg oral suspension twice daily for 16 days) increased the Cmax and AUC of sirolimus (2 mg single dose) an average of 6.7-fold and 8.9-fold, respectively, in healthy subjects. When initiating therapy in patients already taking sirolimus, the dose of sirolimus should be reduced (e.g., to about 1/10 of the current dose) with frequent monitoring of sirolimus whole blood trough concentrations. Sirolimus concentrations should be performed upon initiation, during coadministration, and at discontinuation of posaconazole treatment, with sirolimus doses adjusted accordingly.

Tacrolimus: Posaconazole has been shown to significantly increase the Cmax and AUC of tacrolimus (0.05 mg/kg single dose) by 121% and 358%, respectively. At initiation of posaconazole treatment, reduce the tacrolimus dose to approximately one-third of the original dose. Frequent monitoring of tacrolimus whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus dose adjusted accordingly.

Cyclosporine: Posaconazole 200mg oral suspension once daily has been shown to increase cyclosporine whole blood concentrations in heart transplant patients upon initiation of posaconazole treatment. It is recommended to reduce cyclosporine dose to approximately three-fourths of the original dose upon initiation of posaconazole treatment. Frequent monitoring of cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the cyclosporine dose adjusted accordingly.

**2. CYP3A4 Substrates**

Concomitant administration of posaconazole with CYP3A4 substrates such as pimozide and quinidine may result in increased plasma concentrations of these drugs, leading to QTc prolongation and rare occurrences of torsades de pointes. Therefore, posaconazole is contraindicated with these drugs.

**3. HMG-CoA Reductase Inhibitors (Statins) Primarily Metabolized Through CYP3A4**

Repeat dose administration of oral posaconazole (50, 100, and 200 mg oral suspension once daily for 13 days) increased the Cmax and AUC of simvastatin (40 mg single dose) an average of 7.4- to 11.4-fold, and 5.7- to 10.6-fold, respectively. Increased HMG-CoA reductase inhibitor concentrations in plasma can be associated with rhabdomyolysis. Coadministration of posaconazole and HMG-CoA reductase inhibitors primarily metabolized through CYP3A4 is contraindicated.

**4. Ergot Alkaloids**

Most of the ergot alkaloids are substrates of CYP3A4. Posaconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism. Therefore, posaconazole is contraindicated with ergot alkaloids.

**5. Benzodiazepines Metabolized by CYP3A4**

Concomitant administration of posaconazole with midazolam increases the midazolam plasma concentrations by approximately 5 fold. Repeat dose administration of oral posaconazole (200 mg oral suspension twice daily for 7 days) increased the Cmax and AUC of IV midazolam (0.4 mg single dose) an average of 1.3- and 4.6-fold, respectively; Posaconazole 400 mg oral suspension twice daily for 7 days increased the IV midazolam $C_{max}$ and AUC by 1.6 and 6.2-fold, respectively. Both doses of posaconazole increased Cmax and AUC of oral midazolam (2 mg single oral dose) by 2.2 and 4.5-fold, respectively. In addition, oral posaconazole (200 mg or 400 mg oral suspension) prolonged the mean terminal half-life of midazolam from approximately 3-4 hours to 8-10 hours during coadministration. Increased plasma midazolam concentrations could potentiate and prolong hypnotic and sedative effects.

Concomitant use of posaconazole and other benzodiazepines metabolized by CYP3A4 (e.g., alprazolam, triazolam) could result in increased plasma concentrations of these benzodiazepines. Patients must be monitored closely for adverse effects associated with high plasma concentrations of benzodiazepines metabolized by CYP3A4 and benzodiazepine receptor antagonists must be available to reverse these effects. It is recommended that dose adjustments of benzodiazepines, metabolized by CYP3A4, be considered during coadministration with posaconazole.

**6. Anti-HIV Drugs**

As HIV protease inhibitors are CYP3A4 substrates, it is expected that posaconazole will increase plasma levels of these antiretroviral agents. Repeat dose administration of oral posaconazole (400 mg oral suspension twice daily for 7 days) increased the Cmax and AUC of atazanavir (300 mg once a day for 7 days) an average of 2.6-fold and 3.7-fold, respectively, in healthy subjects. Repeat dose administration of oral posaconazole (400 mg oral suspension twice daily for 7 days) increased the $C_{max}$ and AUC of atazanavir to a lesser extent when administered as a boosted regimen with ritonavir (300 mg atazanavir plus ritonavir 100 mg once a day for 7 days) with an average of 1.5-fold and 2.5-fold, respectively, in healthy subjects. Frequent monitoring for adverse events and toxicity related to antiretroviral agents that are substrates of CYP3A4 is recommended during co-administration with posaconazole.

Efavirenz: Efavirenz induces UDP-glucuronidase and significantly decreases posaconazole plasma concentrations. 400mg once a day decreased the Cmax and AUC of posaconazole by 45% and 50%, respectively. It is recommended to avoid concomitant use of efavirenz with posaconazole unless the benefit outweighs the risks.

Ritonavir and Atazanavir: Ritonavir and atazanavir are metabolized by CYP3A4 and posaconazole increases plasma concentrations of these drugs. Frequent monitoring of adverse effects and toxicity of ritonavir and atazanavir should be performed during coadministration with posaconazole.

Fosamprenavir: Combining fosamprenavir with posaconazole may lead to decreased posaconazole plasma concentrations. If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended. Repeat dose administration of fosamprenavir (700 mg BID x 10 days) decreased the $C_{max}$ and AUC of posaconazole (200 mg oral suspension QD on the 1st day, 200 mg oral suspension BID on the 2nd day, then 400 mg oral suspension BID x 8 Days) by 21% and 23%, respectively.

**7. Rifabutin**

Rifabutin induces UDP-glucuronidase, Rifabutin 300mg once a day decreased the $C_{max}$ and AUC of posaconazole by 43% and 49%, respectively. Rifabutin is also metabolized by CYP3A4. Therefore, coadministration of rifabutin with posaconazole increases the Cmax and AUC of rifabutin by 31% and 72%, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the

benefit to the patient outweighs the risk. However, if concomitant administration is required, close monitoring for breakthrough fungal infections as well as frequent monitoring of full blood counts and adverse reactions due to increased rifabutin plasma concentrations (e.g., uveitis, leukopenia) are recommended.

**8. Phenytoin**

Phenytoin induces UDP-glucuronidase, Phenytoin 200mg once a day decreased the $C_{max}$ and AUC of posaconazole by 41% and 50%, respectively. Phenytoin is also metabolized by CYP3A4. Therefore, coadministration of phenytoin with posaconazole increases phenytoin plasma concentrations. Concomitant use of posaconazole and phenytoin should be avoided unless the benefit to the patient outweighs the risk. However, if concomitant administration is required, close monitoring for breakthrough fungal infections is recommended and frequent monitoring of phenytoin concentrations should be performed while coadministered with posaconazole and dose reduction of phenytoin should be considered.

**9. Gastric Acid Suppressors/Neutralizers**

Cimetidine (an H2-receptor antagonist) and esomeprazole (a proton pump inhibitor) decrease posaconazole plasma concentrations. It is recommended to avoid concomitant use of cimetidine and esomeprazole with posaconazole unless the benefit outweighs the risks.

Posaconazole plasma concentrations (Cmax and AUC) were reduced by 39 % when posaconazole oral suspension was administered with cimetidine (400 mg twice a day) due to reduced absorption possibly secondary to a decrease in gastric acid production. Co-administration of posaconazole oral suspension with H2 receptor antagonists should be avoided if possible.

Similarly, administration of 400 mg posaconazole oral suspension with esomeprazole (40 mg daily) decreased mean Cmax and AUC by 46 % and 32 %, respectively, compared to dosing with 400 mg posaconazole alone. Co-administration of posaconazole oral suspension with proton pump inhibitors should be avoided if possible.

However, if concomitant administration is required, close monitoring for breakthrough fungal infections is recommended. No clinically relevant effects were observed when posaconazole is concomitantly used with antacids and H2-receptor antagonists other than cimetidine. No dosage adjustment of posaconazole is required when posaconazole is concomitantly used with antacids and H2 receptor antagonists other than cimetidine.

**10. Vinca Alkaloids**

Most of the vinca alkaloids are substrates of CYP3A4. Posaconazole may increase the plasma concentrations of vinca alkaloids (e.g., vincristine and vinblastine) which may lead to neurotoxicity. Therefore, it is recommended that dose adjustment of the vinca alkaloid be considered.

**11. Calcium Channel Blockers Metabolized by CYP3A4**

Posaconazole may increase the plasma concentrations of calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, diltiazem, nifedipine, nicardipine, felodipine). Frequent monitoring for adverse reactions and toxicity related to calcium channel blockers is recommended during coadministration. Dose reduction of calcium channel blockers may be needed.

**12. Digoxin**

Increased plasma concentrations of digoxin have been reported in patients receiving digoxin and posaconazole. Therefore, monitoring of digoxin plasma concentrations is recommended during coadministration.

**13. Gastrointestinal Motility Agents**

Metoclopramide decreases posaconazole plasma concentrations. If metoclopramide is concomitantly administered, it is recommended to closely monitor for breakthrough fungal infections.

Loperamide does not affect posaconazole plasma concentrations. No dosage adjustment of posaconazole is required when loperamide and posaconazole are used concomitantly.

**14. Glipizide**

10mg single dose had no clinically significant effect on posaconazole $C_{max}$ and AUC. Although no dosage adjustment of glipizide is required, it is recommended to monitor glucose concentrations when posaconazole and glipizide are concomitantly used.

**15. Zidovudine (AZT), lamivudine (3TC), indinavir**

Clinical studies demonstrated that no clinically significant effects on zidovudine, lamivudine, indinavir were observed when administered with posaconazole; therefore, no dose adjustments are required for these co-administered drugs.

**[Overdosage]**

During the clinical trials, some patients received posaconazole up to 1600 mg/day with no adverse reactions noted that were different from the lower doses. In addition, accidental overdose was noted in one patient who took 1200 mg BID for 3 days. No related adverse reactions were noted by the investigator.

Posaconazole is not removed by hemodialysis.

**[Clinical Trial]**

**1. Prophylaxis of *Aspergillus* and *Candida* Infections**

Two randomized, controlled studies were conducted using posaconazole as prophylaxis for the prevention of invasive fungal infections (IFIs) among patients at high risk due to severely compromised immune systems.

The first study (Study 1) was a randomized, double-blind trial that compared posaconazole oral suspension (200 mg three times a day) with fluconazole capsules (400 mg once daily) as prophylaxis against invasive fungal infections in allogeneic hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD). Efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic antifungal therapy (patients may have met more than one of these criteria). Study 1 assessed all patients while on study therapy plus 7 days and at 16 weeks post-randomization. The mean duration of therapy was comparable between the 2 treatment groups (80 days, posaconazole; 77 days, fluconazole). Table 6 contains the results from Study 1.

TABLE 6: Results from Blinded Clinical Study 1 in Prophylaxis of IFI in All Randomized Patients with Hematopoietic Stem Cell Transplant (HSCT) and Graft-vs.-Host Disease (GVHD)

| | **Posaconazole n=301** | **Fluconazole n=299** |
|---|---|---|
| ***On therapy plus 7 days*** | | |
| **Clinical Failure*** | 50 (17%) | 55 (18%) |
| **Failure due to:** | | |
| Proven/Probable IFI | 7 (2%) | 22 (7%) |
| (*Aspergillus*) | 3 (1%) | 17 (6%) |
| (*Candida*) | 1 (<1%) | 3 (1%) |
| (Other) | 3 (1%) | 2 (1%) |
| All Deaths | 22 (7%) | 24 (8%) |
| Proven/probable fungal infection prior to death | 2 (<1%) | 6 (2%) |
| SAF† | 27 (9%) | 25 (8%) |
| ***Through 16 weeks*** | | |
| **Clinical Failure*,‡** | 99 (33%) | 110 (37%) |
| **Failure due to:** | | |
| Proven/Probable IFI | 16 (5%) | 27 (9%) |
| (*Aspergillus*) | 7 (2%) | 21 (7%) |
| (*Candida*) | 4 (1%) | 4 (1%) |
| (Other) | 5 (2%) | 2 (1%) |
| All Deaths | 58 (19%) | 59 (20%) |
| Proven/probable fungal infection prior to death | 10 (3%) | 16 (5%) |
| SAF† | 26 (9%) | 30 (10%) |
| Event free lost to follow-up§ | 24 (8%) | 30 (10%) |

* Patients may have met more than one criterion defining failure.
† Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >4 consecutive days).
‡ 95% confidence interval (posaconazole-fluconazole) = (-11.5%, +3.7%).
§ Patients who are lost to follow-up (not observed for 112 days), and who did not meet another clinical failure endpoint. These patients were considered failures.

The second study (Study 2) was a randomized, open-label study that compared posaconazole oral suspension (200 mg 3 times a day) with fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) as prophylaxis against IFIs in neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes. As in Study 1, efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic antifungal therapy (Patients might have met more than one of these criteria). Study 2 assessed patients while on treatment plus 7 days and 100 days postrandomization. The mean duration of therapy was comparable between the 2 treatment groups (29 days, posaconazole; 25 days, fluconazole or itraconazole). Table 7 contains the results from Study 2.

TABLE 7: Results from Open-Label Clinical Study 2 in Prophylaxis of IFI in All Randomized Patients with Hematologic Malignancy and Prolonged Neutropenia

| | **Posaconazole n=304** | **Fluconazole/Itraconazole n=298** |
|---|---|---|
| ***On therapy plus 7 days*** | | |
| **Clinical Failure**[*,†] | 82 (27%) | 126 (42%) |
| **Failure due to:** | | |
| Proven/Probable IFI | 7 (2%) | 25 (8%) |
| (*Aspergillus*) | 2 (1%) | 20 (7%) |
| (*Candida*) | 3 (1%) | 2 (1%) |
| (Other) | 2 (1%) | 3 (1%) |
| All Deaths | 17 (6%) | 25 (8%) |
| Proven/probable fungal infection prior to death | 1 (<1%) | 2 (1%) |
| SAF[‡] | 67 (22%) | 98 (33%) |
| ***Through 100 days postrandomization*** | | |
| **Clinical Failure**[†] | 158 (52%) | 191 (64%) |
| **Failure due to:** | | |
| Proven/Probable IFI | 14 (5%) | 33 (11%) |
| (*Aspergillus*) | 2 (1%) | 26 (9%) |
| (*Candida*) | 10 (3%) | 4 (1%) |
| (Other) | 2 (1%) | 3 (1%) |
| All Deaths | 44 (14%) | 64 (21%) |
| Proven/probable fungal infection prior to death | 2 (1%) | 16 (5%) |
| SAF[‡] | 98 (32%) | 125 (42%) |
| Event free lost to follow-up[§] | 34 (11%) | 24 (8%) |

* 95% confidence interval (posaconazole-fluconazole/itraconazole) = (-22.9%, -7.8%).
† Patients may have met more than one criterion defining failure.
‡ Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >3 consecutive days).
§ Patients who are lost to follow-up (not observed for 100 days), and who did not meet another clinical failure endpoint. These patients were considered failures.

In summary, 2 clinical studies of prophylaxis were conducted. As seen in the accompanying tables (Tables 6 and 7), clinical failure represented a composite endpoint of breakthrough IFI, mortality and use of systemic antifungal therapy. In Study 1 (Table 6), the clinical failure rate of posaconazole (33%) was similar to fluconazole (37%), (95% CI for the difference posaconazole–comparator -11.5% to 3.7%) while in Study 2 (Table 7) clinical failure was lower for patients treated with posaconazole (27%) when compared to patients treated with fluconazole or itraconazole (42%), (95% CI for the difference posaconazole–comparator -22.9% to -7.8%).

All-cause mortality was similar at 16 weeks for both treatment arms in Study 1 [POS 58/301 (19%) vs. FLU 59/299 (20%)]; all-cause mortality was lower at 100 days for posaconazole-treated patients in Study 2 [POS 44/304 (14%) vs. FLU/ITZ 64/298 (21%)]. Both studies demonstrated substantially fewer breakthrough infections caused by Aspergillus species in patients receiving posaconazole prophylaxis when compared to patients receiving fluconazole or itraconazole.

**2. Treatment of Oropharyngeal Candidiasis**

Study 3 was a randomized, controlled, evaluator-blinded study in HIV-infected patients with oropharyngeal candidiasis. Patients were treated with posaconazole or fluconazole oral suspension

(both posaconazole and fluconazole were given as follows: 100 mg twice a day for 1 day followed by 100 mg once a day for 13 days).

Clinical and mycological outcomes were assessed after 14 days of treatment and at 4 weeks after the end of treatment. Patients who received at least 1 dose of study medication and had a positive oral swish culture of Candida species at baseline were included in the analyses (see Table 8). The majority of the subjects had C. albicans as the baseline pathogen.

Clinical success at Day 14 (complete or partial resolution of all ulcers and/or plaques and symptoms) and clinical relapse rates (recurrence of signs or symptoms after initial cure or improvement) 4 weeks after the end of treatment were similar between the treatment arms (see Table 8).

Mycologic eradication rates (absence of colony forming units in quantitative culture at the end of therapy, Day 14), as well as mycologic relapse rates (4 weeks after the end of treatment) were also similar between the treatment arms (see Table 8).

TABLE 8: Clinical Success, Mycological Eradication, and Relapse Rates in Oropharyngeal Candidiasis

| | **Posaconazole** | **Fluconazole** |
|---|---|---|
| Clinical Success at End of Therapy (Day 14) | 155/169 (91.7%) | 148/160 (92.5%) |
| Clinical Relapse (4 Weeks after End of Therapy) | 45/155 (29.0%) | 52/148 (35.1%) |
| Mycological Eradication (absence of CFU) at End of Therapy (Day 14) | 88/169 (52.1%) | 80/160 (50.0%) |
| Mycological Relapse (4 Weeks after End of Treatment) | 49/88 (55.6%) | 51/80 (63.7%) |

Mycologic response rates, using a criterion for success as a posttreatment quantitative culture with ≤20 colony forming units (CFU/mL) were also similar between the two groups (posaconazole 68.0%, fluconazole 68.1%). The clinical significance of this finding is unknown.

### 3. Treatment of Oropharyngeal Candidiasis Refractory to Treatment with Fluconazole or Itraconazole

Study 4 was a noncomparative study of posaconazole oral suspension in HIV-infected subjects with OPC that was refractory to treatment with fluconazole or itraconazole. An episode of OPC was considered refractory if there was failure to improve or worsening of OPC after a standard course of therapy with fluconazole ≥100 mg/day for at least 10 consecutive days or itraconazole 200 mg/day for at least 10 consecutive days and treatment with either fluconazole or itraconazole had not been discontinued for more than 14 days prior to treatment with posaconazole. Of the 199 subjects enrolled in this study, 89 subjects met these strict criteria for refractory infection.

Forty-five subjects with refractory OPC were treated with posaconazole 400 mg BID for 3 days, followed by 400 mg QD for 25 days with an option for further treatment during a 3-month maintenance period. Following a dosing amendment, a further 44 subjects were treated with posaconazole 400 mg BID for 28 days. The efficacy of posaconazole was assessed by the clinical success (cure or improvement) rate after 4 weeks of treatment. The clinical success rate was 74.2% (66/89). The clinical success rates for both the original and the amended dosing regimens were similar (73.3% and 75.0%, respectively).

**[Pharmacology & Toxicology]**

**Pharmacology**

Mechanism of Action

Posaconazole is a triazole antifungal agent. Posaconazole is a potent inhibitor of the enzyme lanosterol 14α-demethylase, which catalyses an essential step in ergosterol biosynthesis. Posaconazole produce antifungal effect through the inhibition of lanosterol 14α-demethylase in the fungal cell membrane.

Microbiology

Posaconazole has been shown *in vitro* and in clinical infections to be active against the following micro-organisms: *Aspergillus* species (*A. fumigatus*, *A. flavus*, *A. terreus*, *A. nidulans*, *A. niger*, *A. ustus, A. ochraceus*), *Candida* species (*C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*), *Cryptococcus neoformans*, *Coccidioides immitis*, *Fonsecaea pedrosoi*, *Histoplasma capsulatum, Pseudallescheria boydii* and species of *Alternaria*, *Exophiala*, *Fusarium*, *Ramichloridium, Rhizomucor*, *Mucor*, and *Rhizopus.*

Posaconazole also exhibits *in vitro* activity against the following yeasts and moulds: *Candida dubliniensis, C. famata, C. guilliermondii, C. lusitaniae, C. kefyr, C. rugosa, C. tropicalis, C. zeylanoides, C. inconspicua, C. lipolytica, C. norvegensis, C. pseudotropicalis, Cryptococcus laurentii, Kluyveromyces marxianus, Saccharomyces cerevisiae, Yarrowia lipolytica,* species of *Pichia*, and *Trichosporon, Aspergillus sydowii, Bjerkandera adusta, Blastomyces dermatitidis, Epidermophyton floccosum, Paracoccidioides brasiliensis, Scedosporium apiospermum, Sporothrix schenckii, Wangiella dermatitidis* and species of *Absidia, Apophysomyces, Bipolaris, Curvularia, Microsporum, Paecilomyces, Penicillium, and Trichophyton*. However, the safety and effectiveness of posaconazole in treating clinical infections due to these microorganisms have not been established in clinical trials.

**NOXAFIL*** exhibits broad-spectrum antifungal activity against some yeasts and moulds not generally responsive to azoles, or resistant to other azoles:

- species of *Candida* (including *C. albicans* isolates resistant to fluconazole, voriconazole and itraconazole, *C. krusei* and *C. glabrata* which are inherently less susceptible to fluconazole, *C. lusitaniae* which is inherently less susceptible to amphotericin B),
- *Aspergillus* (including isolates resistant to fluconazole, voriconazole, itraconazole and amphotericin B)
- organisms not previously regarded as being susceptible to azoles such as thezygomycetes (e.g. species of *Absidia*, *Mucor*, *Rhizopus* and *Rhizomucor*).

*In vitro* **NOXAFIL*** exhibited fungicidal activity against species of:

- *Aspergillus*,
- dimorphic fungi (*Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Penicillium marneffei, Coccidioides immitis*)
- some species of *Candida*.

In animal infection models **NOXAFIL*** was active against a wide variety of fungal infections caused by moulds or yeasts. However, there was no consistent correlation between minimum inhibitory concentration and efficacy.

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted

before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly. Drug Resistance

*C. albicans* strains resistant to posaconazole could not be generated in the laboratory; spontaneous laboratory *Aspergillus fumigatus* mutants exhibiting a decrease in susceptibility to posaconazole arose at a frequency of 1x10-8 to 1x10-9. Clinical isolates of *Candida albicans* and *Aspergillus fumigatus* exhibiting significant decreases in posaconazole susceptibility are rare. In those rare instances where decreased susceptibility was noted, there was no clear correlation between decreased susceptibility and clinical failure. Clinical success has been observed in patients infected with organisms resistant to other azoles; consistent with these observations posaconazole was active in vitro against many *Aspergillus* and *Candida* strains that developed resistance to other azoles and/or amphotericin B. Breakpoints for posaconazole have not been established for any fungi.

*ANTIFUNGAL MEDICINAL PRODUCT COMBINATIONS*

When combinations of posaconazole with either amphotericin B or caspofungin were tested *in vitro* and *in vivo* there was little or no antagonism and in some instances there was an additive effect. The clinical significance of these results is unknown.

**Toxicology**

*Genotoxicity:*

Posaconazole was not genotoxic or clastogenic when evaluated in bacterial mutagenicity (Ames), a chromosome aberration study in human peripheral blood lymphocytes, a Chinese hamster ovary cell mutagenicity study, and a mouse bone marrow micronucleus study.

*Fertility:*

Posaconazole had no effect on fertility of male rats at a dose up to 180 mg/kg (1.7 x the 400-mg BID regimen based on steady-state plasma concentrations in healthy volunteers) or female rats at a dose up to 45 mg/kg (2.2 x the 400-mg BID regimen).

Posaconazole has been shown to cause skeletal malformations (cranial malformations and missing ribs) in rats when given in doses ≥27 mg/kg (≥1.4 times the 400-mg BID regimen based on steady-state plasma concentrations of drug in healthy volunteers). The no-effect dose for malformations in rats was 9 mg/kg, which is 0.7 times the exposure achieved with the 400-mg BID regimen. No malformations were seen in rabbits at doses up to 80 mg/kg. In the rabbit, the no-effect dose was 20 mg/kg, while high doses of 40 mg/kg and 80 mg/kg, 2.9 or 5.2 times the exposure achieved with the 400-mg BID regimen, caused an increase in resorptions. In rabbits dosed at 80 mg/kg, a reduction in body weight gain of females and a reduction in litter size were seen.

Reproduction, peri- and postnatal development studies were conducted in rats. At exposures lower than those obtained at therapeutic doses in humans, posaconazole caused skeletal variations and malformations, dystocia, increased length of gestation, reduced mean litter size and postnatal viability. In rabbits, posaconazole was embryotoxic at exposures greater than those obtained at therapeutic doses. As observed with other azole antifungal agents, these effects on reproduction were considered to be due to a treatment-related effect on steroidogenesis.

*Carcinogenesis:*

No drug-related neoplasms were recorded in rats or mice treated with posaconazole for 2 years at doses higher than the clinical dose. In a 2-year carcinogenicity study, rats were given posaconazole orally at doses up to 20 mg/kg (females), or 30 mg/kg (males). These doses are equivalent to 3.9 or 3.5 times the exposure achieved with a 400-mg BID regimen, respectively, based on steady-state AUC in healthy volunteers administered a high-fat meal (400-mg BID regimen). In the mouse study,

mice were treated at oral doses up to 60 mg/kg/day or 4.8 times the exposure achieved with a 400-mg BID regimen.

*Others:*

As observed with other azole antifungal agents, effects related to inhibition of steroid hormone synthesis were seen in repeated-dose toxicity studies with posaconazole. Adrenal suppressive effects were observed in toxicity studies in rats and dogs at exposures equal to or greater than those obtained at therapeutic doses in humans.

Neuronal phospholipidosis occurred in dogs dosed for ≥ 3 months at lower systemic exposures than those obtained at therapeutic doses in humans. This finding was not seen in monkeys dosed for one year. In twelve-month neurotoxicity studies in dogs and monkeys, no functional effects were observed on the central or peripheral nervous systems at systemic exposures greater than those achieved therapeutically.

Pulmonary phospholipidosis resulting in dilatation and obstruction of the alveoli was observed in the 2-year study in rats. These findings are not necessarily indicative of a potential for functional changes in humans.

No effects on electrocardiograms, including QT and QTc intervals, were seen in a repeat dose safety pharmacology study in monkeys at systemic exposures 4.6-fold greater than the exposures obtained at therapeutic doses in humans. Echocardiography revealed no indication of cardiac decompensation in a repeat dose safety pharmacology study in rats at a systemic exposure 1.4-fold greater than that achieved therapeutically. Increased systolic and arterial blood pressures (up to 29 mm-Hg) were seen in rats and monkeys at systemic exposures 1.4-fold and 4.6-fold greater, respectively, than those achieved with therapeutic doses.

**[Pharmacokinetics]**

Posaconazole is a triazole antifungal agent.

Exposure Response Relationship: In clinical studies of immunocompromised patients, a wide range of plasma exposures to posaconazole was noted. A pharmacokinetic-pharmacodynamic analysis of patient data revealed an apparent association between average posaconazole concentrations (Cav) and prophylactic efficacy. A lower Cav may be associated with an increased risk of treatment failure [defined in the study as treatment discontinuation, use of empiric systemic antifungal therapy (SAF), or invasive fungal infections (IFI)].

To enhance the oral absorption of posaconazole and optimize plasma concentrations:

1) Each dose of NOXAFIL should be administered during or immediately (i.e., within 20 minutes) following a full meal. In patients who cannot eat a full meal, each dose of NOXAFIL should be administered with a liquid nutritional supplement or an acidic carbonated beverage. For patients who cannot eat a full meal or tolerate an oral nutritional supplement or an acidic carbonated beverage, alternative antifungal therapy should be considered or patients should be monitored closely for breakthrough fungal infections.
2) Patients who have severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections.
3) Coadministration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections [see Drug Interactions].

**Absorption:**

In clinical studies of immunocompromised patients, a wide range of plasma exposures to posaconazole was noted. A pharmacokinetic-pharmacodynamic analysis of patient data revealed an apparent association between average posaconazole concentrations (Cav) and prophylactic efficacy. A lower Cav may be associated with an increased risk of treatment failure [defined in the study as treatment discontinuation, use of empiric systemic antifungal therapy (SAF), or invasive fungal infections (IFI)].

Posaconazole is absorbed with a median $T_{max}$ of ~3 to 5 hours. Dose proportional increases in plasma exposure (AUC) to posaconazole were observed following single oral doses from 50 mg to 800 mg and following multiple-dose administration from 50 mg BID to 400 mg BID. No further increases in exposure were observed when the dose was increased from 400 mg BID to 600 mg BID in febrile neutropenic patients or those with refractory invasive fungal infections. Steady-state plasma concentrations are attained at 7 to 10 days following multiple-dose administration.

Following single-dose administration of 200 mg, the mean AUC and $C_{max}$ of posaconazole are approximately 3 times higher when administered with a nonfat meal and approximately 4 times higher when administered with a high-fat meal (~50 gm fat) relative to the fasted state. Following single-dose administration of 400 mg, the mean AUC and Cmax of posaconazole are approximately 3 times higher when administered with a liquid nutritional supplement (14 gm fat) relative to the fasted state (see Table 9). In order to assure attainment of adequate plasma concentrations, it is recommended to administer posaconazole with food or a nutritional supplement.

TABLE 9: The Mean (%CV) [min-max] Posaconazole Pharmacokinetic Parameters Following Single-Dose Suspension Administration of 200 mg and 400 mg Under Fed and Fasted Conditions

| Dose (mg) | $C_{max}$ (ng/mL) | $T_{max}$ * (hr) | AUC (I) (ng·hr/mL) | CL/F (L/hr) | $t_{½}$ (hr) |
|---|---|---|---|---|---|
| 200 mg fasted (n=20)‡ | 132 (50) [45-267] | 3.50 [1.5-36†] | 4179 (31) [2705-7269] | 51 (25) [28-74] | 23.5 (25) [15.3-33.7] |
| 200 mg nonfat (n=20)‡ | 378 (43) [131-834] | 4 [3-5] | 10,753 (35) [4579-17,092] | 21 (39) [12-44] | 22.2 (18) [17.4-28.7] |
| 200 mg high fat (54 gm fat) (n=20)‡ | 512 (34) [241-1016] | 5 [4-5] | 15,059 (26) [10,341-24,476] | 14 (24) [8.2-19] | 23.0 (19) [17.2-33.4] |
| 400 mg fasted (n=23)§ | 121 (75) [27-366] | 4 [2-12] | 5258 (48) [2834-9567] | 91 (40) [42-141] | 27.3 (26) [16.8-38.9] |
| 400 mg with liquid nutritional supplement (14 gm fat) (n=23)§ | 355 (43) [145-720] | 5 [4-8] | 11,295 (40) [3865-20,592] | 43 (56) [19-103] | 26.0 (19) [18.2-35.0] |

* Median [min-max].
† The subject with $T_{max}$ of 36 hrs had relatively constant plasma levels over 36 hrs (1.7 ng/mL difference between 4 hrs and 36 hrs).
‡ n=15 for AUC (I), CL/F, and $t_{½}$
§ n=10 for AUC (I), CL/F, and $t_{½}$

Table 10: The Effect of Varying Gastric Administration Conditions on the $C_{max}$ and AUC of Posaconazole in Healthy Volunteers

| **Study Description** | **Administration Arms** | **Change in $C_{max}$** (ratio estimate**; 90% CI of the ratio estimate) | **Change in AUC** (ratio estimate**; 90% CI of the ratio estimate) |
|---|---|---|---|
| 400-mg single dose with a high-fat meal relative to fasted state (n=12) | 5 minutes before high-fat meal | ↑96% (1.96; 1.48-2.59) | ↑111% (2.11; 1.60-2.78) |
| | During high-fat meal | ↑339% (4.39; 3.32-5.80) | ↑382% (4.82; 3.66-6.35) |
| | 20 minutes after high-fat meal | ↑333% (4.33; 3.28-5.73) | ↑387% (4.87; 3.70-6.42) |
| 400 mg BID and 200 mg QID for 7 days in fasted state and with liquid nutritional supplement (BOOST®) ( n=12) | 400 mg BID with BOOST | ↑65% (1.65; 1.29-2.11) | ↑66% (1.66; 1.30-2.13) |
| | 200 mg QID with BOOST | No Effect | No Effect |
| Divided daily dose from 400 mg BID to 200 mg QID for 7 days regardless of fasted conditions or with BOOST (n=12) | Fasted state | ↑136% (2.36; 1.84-3.02) | ↑161% (2.61; 2.04-3.35) |
| | With BOOST | ↑137% (2.37; 1.86-3.04) | ↑157% (2.57; 2.00-3.30) |
| 400-mg single dose with carbonated acidic beverage (ginger ale) and/or proton pump inhibitor (esomeprazole) (n=12) | Ginger ale | ↑92% (1.92; 1.51-2.44) | ↑70% (1.70; 1.43-2.03) |
| | Esomeprazole | ↓32% (0.68; 0.53-0.86) | ↓30% (0.70; 0.59-0.83) |
| 400-mg single dose with a prokinetic agent (metoclopramide 10 mg TID for 2 days) + BOOST or a antikinetic agent (loperamide 4-mg single dose) + BOOST (n=12) | With metoclopramide + BOOST | ↓21% (0.79; 0.72-0.87) | ↓19% (0.81; 0.72-0.91) |
| | With loperamide + BOOST | ↓3% (0.97; 0.88-1.07) | ↑11% (1.11; 0.99-1.25) |
| 400-mg single dose either orally with BOOST or via an NG tube with BOOST (n=16) | Via NG tube* | ↓19% (0.81; 0.71-0.91) | ↓23% (0.77; 0.69-0.86) |
| *In 5 subjects, the Cmax and AUC decreased substantially (range: -27% to -53% and -33% to -51%, respectively) when NOXAFIL was administered via an NG tube compared to when NOXAFIL was administered orally. It is recommended to closely monitor patients for breakthrough fungal infections when NOXAFIL is administered via an NG tube because a lower plasma exposure may be associated with an increase risk of treatment failure.<br>**Ratio Estimate is the ratio of coadministered drug plus posaconazole to coadministered drug alone for Cmax or AUC. | | | |

The mean (%CV) [min-max] posaconazole average steady-state plasma concentrations (Cav) and steady-state pharmacokinetic parameters in patients following administration of 200 mg TID and 400 mg BID of the oral suspension are provided in Table 11.

TABLE 11: The Mean (%CV) [min-max] Posaconazole Steady-State Pharmacokinetic Parameters in Patients Following Oral Administration of Posaconazole 200 mg TID and 400 mg BID

| Dose* | Cav (ng/mL) | AUC‖ (ng·hr/mL) | CL/F (L/hr) | V/F (L) | t½ (hr) |
|---|---|---|---|---|---|
| 200 mg TID† (n=252) | 1103 (67) [21.5-3650] | ND¶ | ND¶ | ND¶ | ND¶ |
| 200 mg TID‡ (n=215) | 583 (65) [89.7-2200] | 15,900 (62) [4100-56,100] | 51.2 (54) [10.7-146] | 2425 (39) [828-5702] | 37.2 (39) [19.1-148] |
| 400 mg BID§ (n=23) | 723 (86) [6.70-2256] | 9093 (80) [1564-26,794] | 76.1 (78) [14.9-256] | 3088 (84) [407-13,140] | 31.7 (42) [12.4-67.3] |

Note: Cav based on observed data; other pharmacokinetic parameters based on estimates from population pharmacokinetic analyses
* Oral suspension administration
† Allogeneic hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease
‡ Neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes
§ Febrile neutropenic patients or patients with refractory invasive fungal infections, Cav n=24 || AUC (0-24 hr) for 200 mg TID and AUC (0-12 hr) for 400 mg BID
¶ Not done
The variability in average plasma posaconazole concentrations in patients was relatively higher than that in healthy subjects.

**Distribution:**

Posaconazole has an apparent volume of distribution of 1774 L, suggesting extensive extravascular distribution and penetration into the body tissues.

Posaconazole is highly protein bound (>98%), predominantly to albumin.

**Metabolism:**

Posaconazole primarily circulates as the parent compound in plasma. Of the circulating metabolites, the majority are glucuronide conjugates formed via UDP glucuronidation (phase 2 enzymes). Posaconazole does not have any major circulating oxidative (CYP450 mediated) metabolites. The excreted metabolites in urine and feces account for ~17% of the administered radiolabeled dose.

Posaconazole is primarily metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. A summary of drugs studied clinically, which affect posaconazole concentrations, is provided in Table 12.

TABLE 12: Summary of the Effect of Coadministered Drugs on Posaconazole in Healthy Volunteers

| **Coadministered Drug (Postulated Mechanism of Interaction)** | **Coadministered Drug Dose/Schedule** | **Posaconazole Dose/Schedule** | **Effect on Bioavailability of Posaconazole** | |
|---|---|---|---|---|
| | | | **Change in Mean $C_{max}$** (ratio estimate*; 90% CI of the ratio estimate) | **Change in Mean AUC** (ratio estimate*; 90% CI of the ratio estimate) |
| Efavirenz (UDP-G Induction) | 400 mg QD × 10 and 20 days | 400 mg (oral suspension) BID × 10 and 20 days | ↓45% (0.55; 0.47-0.66) | ↓ 50% (0.50; 0.43-0.60) |
| Fosamprenavir (unknown mechanism) | 700 mg BID x 10 days | 200 mg QD on the 1st day, 200 mg BID on the 2nd day, then 400 mg BID x 8 Days | ↓ 21% 0.79 (0.71-0.89) | ↓ 23% 0.77 (0.68-0.87) |
| Rifabutin (UDP-G Induction) | 300 mg QD x 17 days | 200 mg (tablets) QD × 10 days | ↓ 43% (0.57; 0.43-0.75) | ↓ 49% (0.51; 0.37-0.71) |
| Phenytoin (UDP-G Induction) | 200 mg QD x 10 days | 200 mg (tablets) QD × 10 days | ↓ 41% (0.59; 0.44-0.79) | ↓ 50% (0.50; 0.36-0.71) |
| Cimetidine (Alteration of Gastric pH) | 400 mg BID × 10 days | 200 mg (tablets) QD × 10 days | ↓ 39% (0.61; 0.53-0.70) | ↓ 39% (0.61; 0.54-0.69) |
| Esomeprazole (Increase in gastric pH) | 40 mg QAM × 3 days | 400 mg (oral suspension) single dose | ↓ 46% (0.54; 0.43-0.69) | ↓ 32% (0.68; 0.57-0.81) |
| Metoclopramide (Increase in gastric motility) | 10 mg TID × 2 days | 400 mg (oral suspension) single dose | ↓ 21% (0.79; 0.72-0.87) | ↓ 19% (0.81; 0.72-0.91) |

* Ratio Estimate is the ratio of coadministered drug plus posaconazole to posaconazole alone for $C_{max}$ or AUC.

In vitro studies with human hepatic microsomes and clinical studies indicate that posaconazole is an inhibitor primarily of CYP3A4. A clinical study in healthy volunteers also indicates that posaconazole is a strong CYP3A4 inhibitor as evidenced by a >5-fold increase in midazolam AUC. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole. A summary of the drugs studied clinically, for which plasma concentrations were affected by posaconazole, is provided in Table 13.

TABLE 13: Summary of the Effect of Posaconazole on Coadministered Drugs in Healthy Volunteers and Patients

| **Coadministered Drug** *(Postulated Mechanism of Interaction is Inhibition of CYP3A4 by posaconazole)* | **Coadministered Drug Dose/Schedule** | **Posaconazole Dose/ Schedule** | **Effect on Bioavailability of Coadministered Drugs** | |
|---|---|---|---|---|
| | | | **Change in Mean $C_{max}$** (ratio estimate*; 90% CI of the ratio estimate) | **Change in Mean AUC** (ratio estimate*; 90% CI of the ratio estimate) |
| Sirolimus | 2-mg single oral dose | 400 mg (oral suspension) BID x 16 days | ↑ 572% (6.72; 5.62-8.03) | ↑ 788% (8.88; 7.26-10.9) |
| Cyclosporin | Stable maintenance dose in heart transplant recipients | 200 mg (tablets) QD x 10 days | ↑ cyclosporine whole blood trough concentrations Cyclosporine dose reductions of up to 29% were required | |
| Tacrolimus | 0.05-mg/kg single oral dose | 400 mg (oral suspension) BID × 7 days | ↑ 121% (2.21; 2.01-2.42) | ↑ 358% (4.58; 4.03-5.19) |
| Simvastatin | 40-mg single oral dose | 100 mg (oral suspension) QD x 13 days | Simvastatin ↑ 841% (9.41, 7.13-12.44) Simvastatin Acid ↑817% (9.17, 7.36-11.43) | Simvastatin ↑931% (10.31, 8.40-12.67) Simvastatin Acid ↑634% (7.34, 5.82-9.25) |
| | | 200 mg (oral suspension) QD x 13 days | Simvastatin ↑1041% (11.41, 7.99-16.29) Simvastatin Acid ↑851% (9.51, 8.15-11.10) | Simvastatin ↑960% (10.60, 8.63-13.02) Simvastatin Acid ↑748% (8.48, 7.04-10.23) |
| Midazolam | 0.4-mg single IV dose† | 200 mg (oral suspension) BID x 7 days | ↑30% (1.3; 1.13-1.48) | ↑362% (4.62; 4.02-5.3) |
| | 0.4-mg single IV dose† | 400 mg (oral suspension) BID x 7 days | ↑62% (1.62; 1.41-1.86) | ↑524% (6.24; 5.43-7.16) |
| | 2-mg single oral dose† | 200 mg (oral suspension) QD x 7 days | ↑169% (2.69; 2.46-2.93) | ↑470% (5.70; 4.82-6.74) |
| | 2-mg single oral dose† | 400 mg (oral suspension) BID x 7 days | ↑138% (2.38; 2.13-2.66) | ↑397% (4.97; 4.46-5.54) |
| Rifabutin | 300 mg QD x 17 days | 200 mg (tablets) QD × 10 days | ↑ 31% (1.31; 1.10-1.57) | ↑72% (1.72;1.51-1.95) |
| Phenytoin | 200 mg QD PO x 10 days | 200 mg (tablets) QD x 10 days | ↑ 16% (1.16; 0.85-1.57) | ↑16% (1.16; 0.84-1.59) |
| Ritonavir | 100 mg QD x 14 days | 400 mg (oral suspension) BID x 7 days | ↑ 49% (1.49; 1.04-2.15) | ↑ 80% (1.8;1.39-2.31) |

| **Coadministered Drug** *(Postulated Mechanism of Interaction is Inhibition of CYP3A4 by posaconazole)* | **Coadministered Drug Dose/Schedule** | **Posaconazole Dose/ Schedule** | **Effect on Bioavailability of Coadministered Drugs** | |
|---|---|---|---|---|
| | | | **Change in Mean $C_{max}$** (ratio estimate*; 90% CI of the ratio estimate) | **Change in Mean AUC** (ratio estimate*; 90% CI of the ratio estimate) |
| Atazanavir | 300 mg QD x 14 days | 400 mg (oral suspension) BID x 7 | ↑155% (2.55; 1.89-3.45) | ↑268% (3.68; 2.89-4.70) |
| Atazanavir/ ritonavir boosted regimen | 300 mg/100 mg QD x14 days | 400 mg (oral suspension) BID x 7 days | ↑53% (1.53; 1.13-2.07) | ↑146% (2.46; 1.93-3.13) |
| *Ratio Estimate is the ratio of coadministered drug plus posaconazole to coadministered drug alone for $C_{max}$ or AUC.<br>† The mean terminal half-life of midazolam was increased from 3 hours to 7 to 11 hours during coadministration with posaconazole. | | | | |

Additional clinical studies demonstrated that no clinically significant effects on zidovudine, lamivudine, indinavir, or caffeine were observed when administered with posaconazole 200 mg QD; therefore, no dose adjustments are required for these coadministered drugs when coadministered with posaconazole 200 mg QD.

**Excretion:**

Posaconazole is eliminated with a mean half-life (t½) of 35 hours (range: 20-66 hours) and a total body clearance (CL/F) of 32 L/hr. Posaconazole is predominantly eliminated in the feces (71% of the radiolabeled dose up to 120 hours) with the major component eliminated as parent drug (66% of the radiolabeled dose). Renal clearance is a minor elimination pathway, with 13% of the radiolabeled dose excreted in urine up to 120 hours (<0.2% of the radiolabeled dose is parent drug).

**[Storage]**

Store at 25°C; excursions permitted to 15°-30°C. Do not freeze.

**[Package Material & Size]**

105 ml of oral suspension in a 123 ml bottle (glass amber type IV) closed with a plastic child-resistant cap (polypropylene) and a measuring spoon (polystyrene) with 2 graduations: 2.5 ml and 5 ml.

1 bottle/box.

**[Shelf Life]**

Unopened container: 24 months

After first opening the container: 4 weeks

**[Approved Specification]**

JX20070128

**[Import Drug License Number]**

H20150065

**[Company]**

CCI
[redacted]

Tel Number: PPD
[redacted]

## 12.11 List of Abbreviations

| Abbreviations | Definitions |
|---|---|
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AMB | Amphotericin B |
| AML | Acute myelogenous leukemia |
| ANC | Absolute neutrophil count |
| AST | Aspartate aminotransferase |
| ASaT | All Subjects as Treated |
| AUC | Area under the curve |
| $AUC_{0\text{-inf}}$ | Area under the plasma concentration-time curve from time 0 extrapolated to infinity |
| $AUC_{0\text{-last}}$ | Area under the plasma concentration-time curve from time 0 to last measurable concentration |
| BMI | Body mass index |
| BP | Blood pressure |
| bpm | Beats per minute |
| $C_{max}$ | Maximum plasma concentration |
| CI | Confidence interval |
| CFR | Code of Federal Regulations |
| CL | Clearance |
| CL/F | Apparent clearance |
| CRF | Case report form |
| CSR | Clinical study report |
| CYP | Cytochrome P-450 |
| D5W | 5% dextrose for injection |
| ECG | Electrocardiogram |
| ECI | Event of Clinical Interest |
| EOT | End Of Trial |
| ERC | Ethical Review Committee |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act |
| FDAMA | Food and Drug Administration Modernization Act |
| FSH | Follicle stimulating hormone |
| GCP | Good Clinical Practices |
| HIV | Human immunodeficiency virus |
| HSCT | Hematopoietic Stem Cell Transplantation |
| hr | Hour |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation of Technical Requirements for Registrationof Pharmaceuticals for Human Use |
| IEC | Independent Ethics Commitee |
| IFI | Invasive fungal infection |
| IRB | Institutional Review Board |
| IRBs/ERCs | Institutional Review Boards/ethics committees |
| IUD | Intrauterine device |
| IV | Intravenous |
| kg | Kilogram |
| L | Liter |
| MDS | Myelodysplastic syndrome |
| mg | Milligrams |

| Abbreviations | Definitions |
|---|---|
| mL | Milliliter |
| NA | N/A Not applicable |
| NOAEL | No observable adverse effect level |
| NOEL | No observed effect level |
| PK/PD | Pharmacokinetic/Pharmacodynamic |
| POS | Posaconazole |
| PP | Per-Protocol |
| QD | Quaque die (once a day) |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SCH | Schering-Plough identification number |
| SD | Standard deviation |
| SOP | Standard operating procedure |
| $t_{1/2}$ | Half-life |
| $t_{max}$ | Time to reach maximum drug concentration |
| $V_d$ | Volume of Distribution |
| ULN | Upper limit of normal |
| V/F | Volume of distribution as a function of bioavailability |
| WBC | White blood cell (count) |

## 13.0 SIGNATURES

### 13.1 Sponsor's Representative

| | |
|---|---|
| TYPED NAME | |
| TITLE | |
| SIGNATURE | |
| DATE SIGNED | |

### 13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

| | |
|---|---|
| TYPED NAME | |
| TITLE | |
| SIGNATURE | |
| DATE SIGNED | |