SUBA-itraconazole versus conventional itraconazole in the treatment of endemic mycoses: a multi-center, open-label, randomized comparative trial

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Record of Protocol Versions

Description	Date	Version #
Initial Version	4 October 2017	1.0
Clarification of Pharmacokinetics; Sponsor Name Revised	15 February 2018	2.0
Addition of LAR Language to Inclusion Criteria (page 8); Addition of Detail to Schematic (page viii); Clarification of Exclusion Criteria and Screening to include no more than 14 days of Antifungal Medications prior to initiation of Study Drug (pages 15 and 16)	27 April 2018	3.0
Addition of Pharmacokinetics on Day 7 Changed Medical Outcomes Study Survey to SF-12 Version 2 Addition of Contact for Mayne Pharma Associate Director Formatting Corrections to Headers	07 June 2018	4.0
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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following *(use applicable regulations depending on study location and sponsor requirements; samples follow)*:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- ICH Efficacy Guideline: E6 R2 Good Clinical Practice (GCP), November 2016 http://www.ich.org

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

SITE INVESTIGATOR

_____ _____
Signature Date

_____
Title

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DRC	Data Review Committee
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IFI	Invasive fungal infection
IRB	Institutional Review Board
ISM	Independent Safety Monitor
JAMA	Journal of the American Medical Association
MedDRA ®	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NCI	National Cancer Institute, NIH, DHHS
NDA	New Drug Application
NEJM	New England Journal of Medicine
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
SAE	Serious Adverse Event/Serious Adverse Experience

SF-12	Short Form 12 Version 2
SOP	Standard Operating Procedure
US	United States
WHO	World Health Organization

PROTOCOL SUMMARY

Title:	**SUBA-itraconazole versus conventional itraconazole in the treatment of endemic mycoses: an open-label comparative trial**
Phase:	IIb
Population:	80 adults infected with one of the endemic mycoses living in the United States, Canada and Central/South America *(Approximately: 40 Histoplasmosis, 20 Coccidioidomycosis, 20 other endemic mycoses)*
Number of Sites:	Approximately 20 total sites in US, Canada, and Central/South America
Study Duration:	This study is estimated to be opened for 18 months after initiation (12 month patient accrual, 6 month treatment period).
Subject Participation	Each participant will be enrolled in the study for 180 days

Objectives:

The objectives of this study are to compare PK, tolerance, safety, and efficacy of SUBA-Itraconazole study drug versus conventional itraconazole in a randomized open-label trial followed by a second stage of continuing open-label study drug.

Stage I - Randomized, Open-Label, Parallel Group

Primary Objective

- PK at Day 14
- Tolerability at Day 42

Secondary Objective

- PK at Day 7
- PK at Day 42
- Efficacy by Day 42
- Safety by Day 42
- QOL (including hospital/ICU visits) Assessments by Day 42

Stage II – Open-Label Extension

Primary Objective

- Efficacy by Day 180
- Tolerability by Day 180

Secondary Objective

- Safety by 180
- QOL (including hospital/ICU visits) Assessments by Day 180

Description of Study Design:

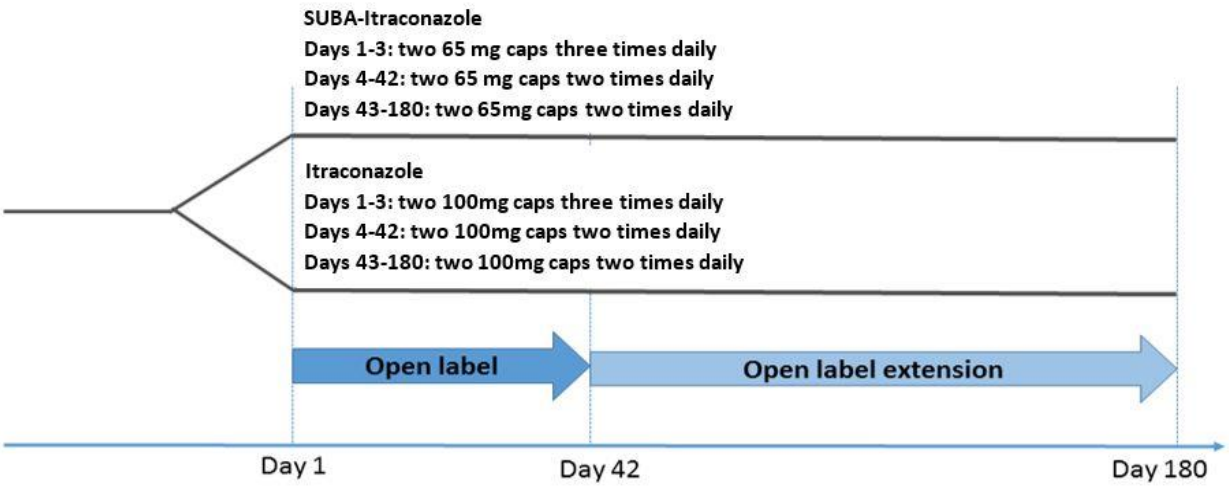
This is a prospective, multi-center, randomized, open-label parallel arm study involving patients with proven or probable invasive endemic fungal infection to ascertain the pharmacokinetics, safety, efficacy, tolerability and health economics of oral SUBA-itraconazole compared to conventional itraconazole. Patients will receive randomized open-label study drug (SUBA-itraconazole or conventional itraconazole) over a 42 day period and then continue therapy until Day 180 or earlier if Principal Investigator determines discontinuation of therapy is safe. Patients will be stratified based on clinically reported infection with the human immunodeficiency virus (HIV).

The study sample size will be 80 evaluable patients – target enrollment (three groups: approximately 40 histoplasmosis, 20 coccidioidomycosis, 20 other endemic fungal infections).

Estimated Time to Complete Enrollment

12 Months

Schematic of Study Design:



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BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

The endemic mycoses are a diverse group of diseases that share several characteristics. They are able to cause disease in otherwise healthy hosts, each pathogen occupies a specific ecologic niche in the environment, are located within a specific geographic region, and exhibit temperature dimorphism – existing as yeasts in the host and molds in the environment [1].

These dimorphic fungi consist of numerous species, however *Histoplasma*, *Coccidioides*, *Paracoccidioides*, *Blastomyces*, *Sporothrix*, and *Talaromyces* (*Penicillium marneffei*) represent the most commonly encountered infections in clinical care. *Histoplasma* spp. are common throughout the Mississippi, Ohio, and St. Lawrence River valleys, the Caribbean, parts of Central and South America, Africa and Asia [2]; *Coccidioides* within the southwestern U.S., and parts of central and South America [3]; *Paracoccidioides* within Central and South America [4]; *Blastomyces* within the Mississippi and Ohio River basins, St Lawrence Seaway, and several Canadian provinces with sporadic cases in Africa, Central and South America [5]; *Sporothrix schenckii* is found worldwide [6]; and *Talaromyces* in Southeast Asia, India, Southern China and Hong Kong [7].

However, the range of the endemic mycoses has been recently questioned and reports describing these pathogens outside of their “known” endemic regions have emerged with increased frequency over the last few years [8-10]. These reports suggest the true incidence and distribution of these fungi may be far greater than previously recognized and thus a much larger population of patients is continually exposed to these pathogens.

Exposure is largely unavoidable for those residing or visiting the endemic regions. Following inhalation these organisms are ingested by pulmonary macrophages yet they frequently are able to survive ingestion and escape, replicate, and thereafter cause disease with ensuing host morbidity and mortality.

The treatment of the endemic mycoses can be difficult for both clinicians and patients. The majority of the endemic mycoses require long courses of antifungal treatment - with courses frequently requiring months to life-long suppressive therapy. Initial therapy for severe disease has traditionally consisted of an amphotericin B formulation and prolonged therapy is limited by the inherent toxicity of polyenes. Following improvement with an amphotericin B formulation, a triazole is prescribed for continuing therapy, usually for a minimum of 6-12 months, depending on the infection.

Currently available agents are limited in the treatment of the endemic fungi by toxicity, poor oral bioavailability [11] or resistance. Fluconazole is widely available yet has limited activity against several of the endemic mycoses including histoplasmosis [12], while in others such as coccidioidomycosis treatment at high doses (> 800 mg/day) is

required, limiting patient tolerability. Voriconazole has been associated with cutaneous malignancy, photosensitivity [13], fluorosis [14], hepatotoxicity, inter-patient pharmacokinetic variability, and has limited activity against *Sporothrix* sp. Itraconazole exhibits variable absorption due to numerous intrinsic and extrinsic factors. In addition, food/acidity requirements are difficult for patients to maintain long-term. Posaconazole solution similarly exhibits dietary requirements and absorption concerns that limit patient compliance and bioavailability [15].

SUBA-itraconazole with twice-daily oral dosing options have improved pharmacokinetics and lack of food/acidity requirements [16].

2.2 Rationale

The availability of SUBA-itraconazole (65 mg capsules) with twice-daily dosing options with improved pharmacokinetics and lack of food/acidity requirements offers a substantial opportunity to improve the treatment of patients with endemic mycoses [16].

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

All medical treatments have the potential of causing undesirable effects. For this reason, the study is performed under carefully controlled conditions.

Common side effects reported to date in patients taking conventional itraconazole (reported in 1-10% of the patients):

- Vomiting
- Diarrhea
- Abdominal pain
- Anorexia
- Edema
- Fatigue
- Fever
- Malaise
- Rash*
- Pruritus
- Headache
- Dizziness
- Libido Decreased
- Somnolence
- Hypertension
- Hypokalemia
- Albuminuria
- Hepatic Function Abnormal
- Impotence

Nausea (11%) is a common side effect (reported in more than 10% of patients) associated with other marketed azoles that may or may not be associated with SUBA-Itraconazole.

Common side effects that were reported in less than 10% of patients taking other marketed azoles (fluconazole, voriconazole, itraconazole, ketoconazole, posaconazole, isavuconazole) were:

- Dizziness
- Chest pain
- Flatulence
- Sleeplessness
- Liver function test abnormalities
- Renal insufficiency
- Trouble Breathing
- Digestion problems
- Tremors
- Asthenia (weakness)
- Cardiovascular problems such as tachycardia or arrhythmia
- Vision disturbances

3 OBJECTIVES

3.1 Study Objectives

The purpose of this study is to compare safety, tolerance, PK, efficacy and cost effectiveness of SUBA-Itraconazole to conventional itraconazole in a randomized, open-label, parallel group trial followed by a second stage (open-label extension) where participants will continue open-label study drug.

3.2 Study Outcome Measures

3.2.1 Primary and Secondary Outcome Measures – Stage I (Open-Label Parallel Group)

Primary Outcomes

- PK at Day 14
- Tolerability at Day 42

Secondary Outcomes

- PK at Day 7
- PK at Day 42
- Efficacy by Day 42
- Safety by Day 42
- QOL (including hospital/ICU visits) Assessments by Day 42

3.2.2 Primary and Secondary Outcome Measures - Stage II (Open-Label Extension)

Primary Outcomes

- Efficacy by Day 180
- Tolerability by Day 180

Secondary Outcomes

- Safety by 180
- QOL (including hospital/ICU visits) Assessments by Day 180

4 STUDY DESIGN

This is a prospective, multi-center, randomized, open-label parallel arm study involving patients with proven or probable invasive endemic fungal infection to ascertain the pharmacokinetics, safety, efficacy, and tolerability of oral SUBA-itraconazole or itraconazole. Patients will receive randomized open-label study drug (either SUBA-itraconazole 65 mg twice daily or itraconazole 100 mg twice daily) over a 42-day period and then continue on their assigned open-label therapy until day 180.

The study sample size will be 80 evaluable patients – target enrollment to include approximately 40 histoplasmosis, 20 coccidioidomycosis, and 20 other endemic fungal infections.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

Subjects must meet all the inclusion criteria in order to be eligible to participate in the study as listed below:

1. Male and female patients age ≥ 18 years who have given written informed consent to participate.
2. Patients who are unresponsive, critically ill, or requiring sedation so they are cognitively impaired will be considered unable to consent for themselves. A Legally Authorized Representative (LAR) will be approached for informed consent. LAR will be determined using this order: (a) legally appointed guardian, (b) health care proxy or authorized individual to make medical decisions in conjunction with a durable power of attorney, (c) spouse, (d) adult child, (e) parent, or (f) next of kin. Qualification of the LAR will be obtained through verbal assurance from the LAR.
3. Patients with a proven or probable endemic mycosis *(Histoplasma*, *Coccidioides*, *Paracoccidioides*, *Blastomyces*, *Sporothrix*, *Talaromyces marneffei* (formerly *Penicillium marneffei*) according to current EORTC/MSG criteria, including patients who:
    - Are immunosuppressed, including as a result of HIV/AIDS
    - Have had a heart, lung or bone marrow transplant
    - Have had chemotherapy for cancer
    - Are otherwise normal hosts

5.2 Subject Exclusion Criteria

All subjects meeting any of these listed exclusion criteria at baseline will be excluded from study participation:

1. Significant liver dysfunction as evidenced by at least 5 times greater than upper limits of normal baseline ALT, AST, alkaline phosphatase, or total bilirubin.
2. Use of an alternative antifungal therapy (IV or oral) for more than 14 days for this infection with the exception of Coccidioidomycosis. Subjects with Coccidioidomycosis who previously received fluconazole therapy for more than 14 days may be included, if in the opinion of the investigator, they are having an inadequate response or, are intolerant of fluconazole (e.g. due to adverse events). Such subjects must washout from fluconazole for 7 days (~5 half-lives of fluconazole) before starting investigational therapy.
3. Evidence of CNS infection.
4. Unable to take PO medications.
5. Female subjects who are lactating or pregnant.

6. Female subjects should be:
   a) Postmenopausal for 1 year,
   b) Post-hysterectomy or bilateral oophorectomy,
   c) If of child bearing potential have a negative β-HCG at screening and using highly effective method of birth control throughout course of study or remain abstinent for duration of study.
7. Male subjects with female partner(s) of child-bearing potential, must agree to use a medically acceptable method of contraception during the study. If their partner is pregnant, males must agree to use a condom; if their partner is of child-bearing potential, their partner must additionally be using one of the following methods: hormonal contraception, intra-uterine device, diaphragm, or cervical cap. Spermicides alone are not an acceptable method of contraception. No sperm donations for 90 days post last dose of study therapy.
8. Documented intolerance, allergy or hypersensitivity to an azole.
9. Inability to comply with study treatment, study visits, and study procedures.
10. Known history of congestive cardiac failure on medical treatment, fungal endocarditis, or other causes of ventricular dysfunction that may outweigh the benefit of itraconazole.
11. Patients with active TB
12. Concurrent use of astemizole, rifampin/rifampicin, rifabutin, ergot alkaloids, long acting barbiturates, carbamazepine, pimozide, quinidine, neostigmine, terfenadine, ketoconazole, valproic acid, or St. John's wort in the 5 days prior to first administration of study drug.
13. Any known or suspected condition of the patient that may jeopardize adherence to the protocol requirements or impede the accurate measurement of efficacy.
14. Treatment with any investigational agent in the 30 days prior to study entry.
15. Patients unlikely to survive 30 days (including severe fungal disease defined by SBP < 90mmHG; hypoxia < 60% saturation).
16. Patients with body weight < 40 kg.

5.3 Treatment Assignment Procedures

5.3.1 Randomization Procedures

Stratified randomization will be used to assign qualifying participants to either conventional itraconazole or SUBA-itraconazole and dosed according to HIV status (positive or negative by clinical self-report) (Section 6.2).
Randomization procedures are described in the Manual of Procedures.

5.3.2 Reasons for Withdrawal

A study subject may be discontinued from participation in the study for the following reasons:

- Any clinical adverse event (AE)
- Withdrawn Consent
- Protocol Violation (e.g., violation of any exclusion criteria)
- Lost to Follow-Up

5.3.3 Handling of Withdrawals

If a subject is withdrawn prior to the end the study, the reason for withdrawal will be documented and entered into the eCRF and if patient is willing to return to be assessed, the End of Treatment (Day 180) assessments will be completed. Documentation of withdrawal in the source documents should include a distinction between participant withdrawal from the study medication regimen and withdrawal from the study itself. In the former case case, the study medication is stopped, but the participant, if willing, continues with study visit assessments; in the latter, study medication and study visit assessments are discontinued.

5.3.4 Termination of Study

This study may be prematurely terminated by the study sponsor or the protocol team for issues related to safety, efficacy, or other reasons (please see Section 5.3.2). If early termination of the study occurs, all study participants will have all End of Treatment (Day 180) assessments completed.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

6.1.1 Acquisition

SUBA-itraconazole and conventional itraconazole will be provided by Mayne Pharma for use in this study. Sites should only use product that has been sourced by Mayne Pharma.

6.1.2 Formulation, Packaging, and Labeling

SUBA-itraconazole Investigator Brochure and conventional itraconazole package insert are provided as separate documents. The conventional itraconazole package insert is also located at:
http://www.janssen.com/us/sites/www_janssen_com_usa/files/products-documents/pi-sporanoxcapsules.pdf)

SUBA-itraconazole study drug will consist of 65 mg capsules.

Conventional itraconazole will consist of 100 mg capsules.

Study drug will be packaged and labeled according to labeling instructions in the Manual of Procedures. Patients will be dispensed study drug by the site with sufficient amount of drug to last through the next study visit plus 5 days. Investigators at each site may determine if the site pharmacy may ship study drug to the participants' homes when clinic visits are not recommended or possible.

Patient initials, Study ID, and date will be recorded on dispensed study record. Documentation of dispensing, including identification of who dispensed the study drug, will be recorded in both the drug accountability log and the patient source documents.

6.1.3 Product Storage and Stability

Both SUBA-itraconazole and conventional itraconazole will be stored according to the guidelines provided in the investigator brochure or package insert, respectively.

6.2 Dosage, Preparation and Administration of Study Intervention/Investigational Product

Study participants will be randomized to receive either open-label SUBA-Itraconazole or conventional itraconazole. Each treatment arm will be dosed as follows:

Arm A: Open-Label SUBA-itraconazole 65 mg Capsules – administered with food

Stage 1

- Day 1 - 3: two 65 mg capsules, three times daily
- Day 4 - 42: two 65 mg capsules, twice daily

Stage 2:

- Day 43 – 180: two 65 mg capsules, twice daily.

Arm B: Conventional Itraconazole 100 mg Capsules – administered with food
Stage 1:

- Day 1 - 3: two 100 mg capsules, three times daily
- Day 4 - 42: two 100 mg capsules, twice daily

Stage 2:

- Day 43 – 180: two 100 mg capsules, twice daily).

Based on standard of care for invasive endemic fungal infection, some participants will be prescribed conventional itraconazole (non-study drug) after Day 180 for up to a year or beyond, as prescribed by their physician. Information for discounted itraconazole will be provided at the end of the study to help defray costs.

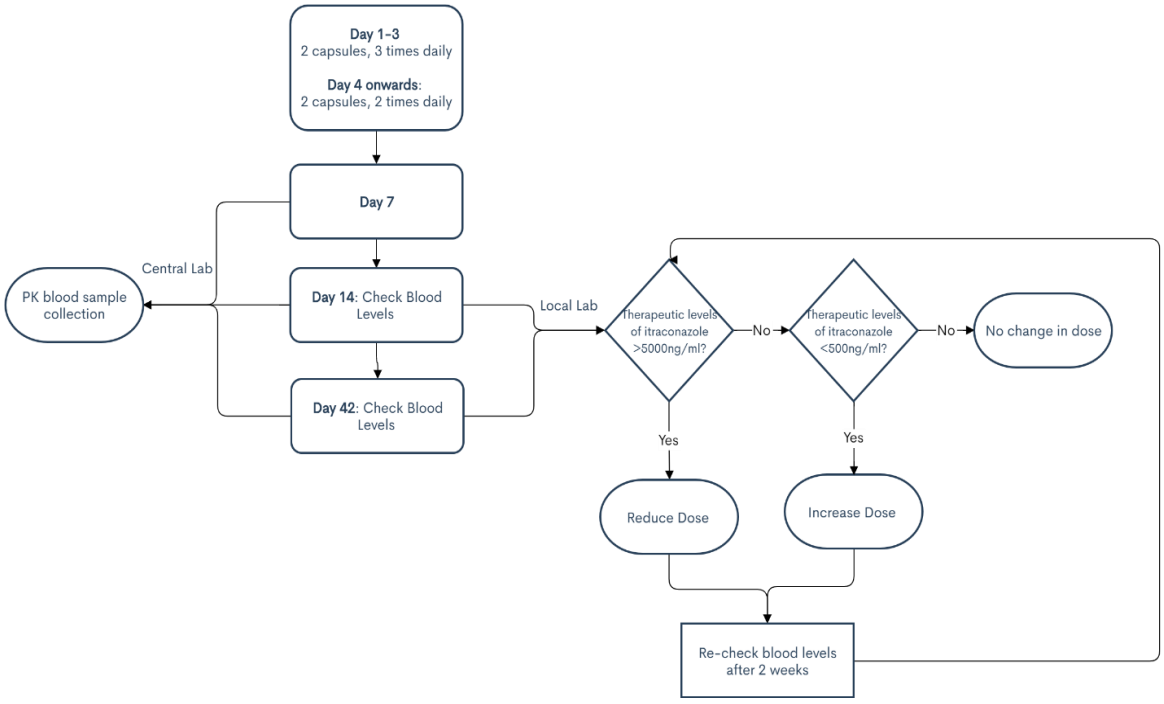
6.3 Modification of Study Intervention/Investigational Product for a Participant

Dose increase, reduction or cessation is permitted at the discretion of the investigator. Any modification to the dosing regimen will be noted in the source document and entered into the eCRF.

The Investigator will consider a dose modification For the following combined drug levels (itraconazole + hydroxyitraconazole) at Day 14 and Day 42:

- <500ng/ml – increase dose
- >5000ng/ml – decrease dose

Any modification to the dosing regimen should have blood-levels re-analyzed every two weeks until the target therapeutic level is achieved (see schema below).



The Investigator will consider dose reduction and/or dose cessation for toxicity if the participant:

- Develops a study drug-related, grade 4 adverse event
- Develops a study drug-related, serious adverse event (SAE)
- Develops dose-limiting study drug-related toxicity despite dose-reduction.

6.4 Accountability and Assessment of Subject Compliance with Study Intervention/Investigational Product

Study drug accountability procedures will be performed by the clinical site. The site will maintain all product per storage guidelines highlighted in the product insert or IB. The clinical site will document receipt, dispensing, and any unused product. This documentation will be maintained throughout the conduct of the study.

Study drug compliance will be assessed at each visit (Day 7, Day 14, Day 28, Day 42, Day 84, Day 180). Subjects will bring all containers and unused medication (if applicable) to each visit. Sites will determine the total amount of product dispensed and compare it to returned product. This information will be collected on the source documents and entered into the eCRF.

6.5 Concomitant Medications/Treatments

6.5.1 Collection

Concomitant medications will be collected from signing of informed consent all the way through to the end of study visit. Any medications taken within 2 weeks of Study Day 1, even if prior to ICF collection date, should be noted.

6.5.2 Restricted Concomitant Medications

Itraconazole may affect the plasma concentration of other drugs, as it is an inhibitor of CYP3A4 as well as P-gp (P-glycoprotein). Sites should carefully evaluate concomitant medication use to ensure that possible drug interactions do not affect the health of the patient.

Drugs that may decrease plasma concentrations of itraconazole include:

Category	**Examples**
Anticonvulsants	carbamazepine, phenobarbital, phenytoin
Antimycobacterials	isoniazid, rifabutin, rifampin
Non-Nucleoside Reverse Transcriptase Inhibitors	nevirapine

GI Medications

Additionally, certain anti-acids, H2 blockers, and protein pump inhibitors are prohibited with conventional itraconazole. If possible, H2 blockers and protein pump inhibitors should be stopped 7 days prior to enrollment, at the discretion of the treating physician. Anti-acids may be taken 1-2 hours AFTER oral dosing with study drug.

Drugs that can increase plasma concentrations of itraconazole include:

Category	**Examples:**
Macrolide Antibiotics	clarithromycin, erythromycin
Protease Inhibitors	indinavir, ritonavir

Alternative fungal medications administered for more than 14 days prior to the first dose of study medication are prohibited unless subject with coccidioidomycosis previously treated with fluconazole therapy for more than 14 days. If in the opinion of the investigator, the subjects with coccidioidomycosis are having an inadequate response or, are intolerant of fluconazole (e.g.due to adverse events), the subjects may be included. Such subjects must washout from fluconazole for 7 days (~5 half-lives of fluconazole) before starting investigational therapy.

7 STUDY SCHEDULE

7.1 Screening

Patients presenting to the clinic or hospital with new onset presumed or definite endemic fungal infection that have not been treated with an alternative antifungal medication for more than 14 days prior to study drug administration; and with no known exclusion criteria by medical history will be given informed consent to enroll in the study.

7.2 Enrollment/Baseline

Patients consenting to the study will be further evaluated for inclusion and exclusion criteria, medical history, physical examination, pregnancy test (blood or urine BHCG), mycologic assessment, antigen and antibody levels, radiography (if clinically indicated); serum chemistry, serum hematology. See Appendix A for study procedures per visit.

7.3 Follow-up

Participants will be assessed in clinic at Day 7, Day 14, Day 28 (1 month), Day 42, Day 84 (3 months) and Day 180 (6 months). In the opinion of the investigator, clinic visits may be replaced with telemedicine visits or home visits, with allowances made for blood draws at remote or commercial laboratories. Documentation in source documents should clearly define accommodations in visit locations or methods when attempting to protect participants and other patients from potential exposure and hazards related to COVID-19.
The Day 7, 14 and 42 visits allow a narrow window (+/- 3 days) so that accurate PK levels can be drawn.

The Day 84 and 180 visits will allow a window of (+/- 7 days).

At each visit, blood samples will be drawn for study-specific safety and efficacy labs. In addition a quality of life questionnaire will be administered at Day 42. See Appendix A for study procedures per visit.

7.4 Final Study Visit or Early Termination Visit

The final study visit will occur at Day 180 (with a window of +/-7 days). During this visit, a physical examination, vital signs, quality of life questionnaire, assessments of concomitant medications and adverse events and mycological assessments will take place. Blood and urine samples will be drawn for study-specific safety and efficacy labs. See Appendix A for study procedures per visit.

7.5 Unscheduled Visit

If clinically indicated, study subjects may be asked to return to clinic to further assess safety issues, resolution of a safety issue, evaluate treatment compliance, or other reasons as determined by the investigator.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

1. *Medical history will be obtained by interview and if available, from medical records.*
2. *Medications history includes medications taken within the prior 2 weeks and indication. Assessment of eligibility should include a review of permitted and prohibited medications.*
3. *Physical examination will be conducted at baseline, targeted physical exams may occur with vital signs at each subsequent visit. At end of therapy or early termination, a physical examination is required.*

8.2 Laboratory Evaluations

Safety laboratory evaluations (Hematology, Biochemistry and Urine Pregnancy Tests) will be conducted by the local site laboratory as part of standard of care for treating patients with endemic mycoses.

8.2.1 Clinical Laboratory Evaluations

8.2.1.1 Hematology: hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.

8.2.1.2 Biochemistry: creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST).

8.2.1.3 Blood or Urine Pregnancy test, to be done within 24 hours prior to study intervention and results must be available prior to administration of study product.

8.2.1.4 HIV: HIV Testing must be performed and resulted no more than 30 days prior to start of study unless previous positive findings are documented in source documents.

8.2.2 Special Assays or Procedures

Antibody and antigen assays for Histoplasmosis, blastomycosis and coccidioidomycoses will be performed at study sites using instructions for specimen handling and processing found in the Manual of Procedures.

Pharmacokinetic assessments to quantify plasma concentrations of itraconazole and hydroxyitraconazole will be performed by a Central Laboratory. Instructions for specimen handling, storage, and shipping are found in the Manual of Procedures.

8.3 Quality of Life (QOL) Evaluations

8.3.1 Short Form 12 Version 2 (SF-12v2)

The SF-12v2 is a 12-question multipurpose survey instrument derived from the larger, SF-36 [17]. The SF-12v2 has been used in numerous healthcare settings and disease types to help determine the patient's overall state of wellbeing and health-related QOL by means of assessing both physical and mental status at the time of the survey. The 8 domains of the survey are: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). Subjects will be administered the SF-12PK at Day 1, Day 42, and Day 180. Version 2 of the SF-12 (Optum) will be used for this study.

8.4 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

8.4.1 Adverse Events

ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for "serious adverse events" should be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include MD, PA, Nurse Practitioner, DO, or DDS), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

All AEs must be graded for severity and relationship to study product.

FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Severity of Event: All AEs will be assessed by the clinician using a protocol defined grading system. For events not included in the protocol defined grading system, than the following guidelines will be used to quantify intensity.

- Mild: events require minimal or no treatment and do not interfere with the patient's daily activities.
- Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Life threatening: any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Relationship to Study Products: The clinician's assessment of an AE's relationship to test article (study drug) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study product assessed using the terms: related or not related. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.4.2 Serious Adverse Events

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- a life-threatening adverse event*,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

* Life-threatening adverse event: an adverse event is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event, had it occurred in a more severe form, might have caused death.

All SAEs will be:

- recorded on the appropriate SAE CRF
- followed through resolution by a study clinician
- reviewed and evaluated by a study clinician

8.5 Reporting Procedures

8.5.1 Serious Adverse Events

AEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form (located in the Manual of Procedures) to the MSG Coordinating Center at the University of Alabama in Birmingham.

Contact:

Alisa Peinhardt
Mycoses Study Group Administrator
University of Alabama at Birmingham, Infectious Diseases Division
1922 7th Avenue South, Kracke Building #731
Birmingham, AL 35233
Phone 205-934-9661
Fax 205-975-9901
Email apeinhardt@uabmc.edu

Other supporting documentation of the event should be provided immediately or as soon as possible.

The Study Principal Investigator will be notified of the SAE by the MSG Coordinating Center and will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the investigator becomes aware of an SAE that is suspected as being related to study product, the investigator will report the event to the MSG Coordinating Center who will notify Mayne Pharma.

8.5.2 Regulatory Reporting

The MSG Coordinating Center, will report any suspected adverse reaction that is both serious and unexpected. The MSG Coordinating Center will report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. The MSG Coordinating Center will notify FDA, Mayne Pharma, and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under the IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. The MSG Coordinating Center will also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, the MSG Coordinating Center will submit to FDA any additional data or information that the

agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All serious events designated as “not related” to study product(s), will be reported to the FDA at least annually in a summary format.

8.6 Safety Oversight (Data Review Committee)

Safety oversight will be under the direction of the study designated Data Review Committee (DRC). The DRC will meet to assess safety and efficacy data on each arm of the study. The DRC will review aggregate safety data for increased rate of occurrence of serious suspected adverse reactions. The DRC will operate under the rules of a charter that will be written at the organizational meeting of the DRC. At this time, each data element that the DRC needs to assess will be clearly defined. The DRC will advise the study team of its findings.

9 CLINICAL MONITORING

9.1 Site Monitoring Plan

Trial monitoring is an integral component of trial quality assurance and critical for ICH GCP fulfillment. According to the International Council for Harmonisation E6 Good Clinical Practice (R2), and the FDA Title 21 CFR, Part 312, Subpart D, Responsibilities of the Sponsor. The sponsor should determine the appropriate extent and nature of monitoring based on the study objectives, purpose, design, complexity, blinding, size and endpoints. ICH states that naturally, there is a need for on-site monitoring, but there are circumstances when remote or central monitoring may be permitted. These regulations incorporated risk-based monitoring in the most recent revision encouraging the sponsor to rationalize the blend of monitoring (on-site, combination of on-site and centralized monitoring, or only remote monitoring).

Risk-based monitoring is defined by the FDA Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring, as focused sponsor oversight activities on preventing or mitigating important and likely risks to data quality and processes critical to human subject protection and trial integrity. The approach the sponsor has approved for this study is a hybrid of on-site and centralized monitoring. Qualification visit will be performed on-site with all the assigned study staff present and facilities inspected. Site Initiation and Training can be performed remotely or on-site, based on the availability of the site staff.

Routine monitoring activities will be performed both on-site periodically, as is possible and safe related to the ongoing COVID-19 precautions, with the primary process being remote monitoring of the regulatory files and electronic case report forms to identify potential issues.

A site monitor will be appointed as an unbiased and independent party to perform various study visits to evaluate the site's capabilities and monitor the ongoing progress of a clinical study. Over the course of the study, the role of the site monitor is to verify the following on behalf of the study team at the appointed site:

- The rights, well-being, and safety of human subjects are protected.
- Reported trial data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved Protocol, GCP, and applicable regulatory requirements.

10 STATISTICAL CONSIDERATIONS

10.1 Study Hypotheses and Statistical Analyses

For the primary outcomes of Stage I, t- and chi-square tests will be used to test whether the treatment group experiences superior PK at Day 14 and Tolerability at Day 42, respectively. If it is determined that the assumptions of the t-test are not met by the data, non-parametric statistical tests will be employed; Fisher's exact test will be used as deemed necessary. In the unusual occurrence that the study groups are not in equipoise with respect to the measured baseline demographic, behavioral and clinical characteristics, linear and logistic regression models will be used to compare the treatment groups, adjusted for any observed differences. The same aforementioned statistics techniques will be used for the secondary outcomes of Stage I as well as the primary and secondary outcomes of Stage II.

10.2 Sample Size Considerations

The study will randomize 80 adults infected with one of the endemic mycoses living in the United States, Canada and Central/South America *(40 Histo, 20 Cocci, 20 other endemic mycoses).* This sample size provides adequate power (77%) to reject the null hypothesis of equal pharmacokinetic means when the population mean difference is μ1 - μ2 = 231.7 - 291.7 = -60.0 with standard deviations of 94.0 and 101.8 for the study groups, and with a significance level (alpha) of 0.050 using a two-sided two-sample unequal-variance t-test.

10.3 Study Outcomes

Stage I- Randomized Open-Label, Parallel Group

Primary Endpoints

1. Pharmacokinetic superiority at Day 14
   a) Inter- and intra- patient variability: Time to attain therapeutic plasma concentrations of itraconazole (> 500 mcg/L)
   b) Interpatient variability as calculated by co-efficient of variation

   Trough (pre-morning dose) sample will be collected at Days 14 and 42.
   Using validated LC-MS/MS methods, blood samples will be analyzed to quantify plasma concentrations of itraconazole and hydroxyitraconazole.

   Participants should arrive to the trial site having **not** taken their morning dose of study drug.

Note: site investigators are discouraged from drawing independent PK laboratories to check itraconazole levels outside of the designated timepoints (Day 14)

2. Tolerability - ability to remain on study drug at Day 42 with less than a 7-day interruption of therapy

Secondary Endpoints

1. PK at day 7 – plasma concentrations of itraconazole- (*comparative trough, steady state plasma itraconazole concentrations of SUBA-itraconazole 65mg capsules with food to itraconazole 100mg capsules with food over 7 days)*
2. PK at day 42 - plasma concentrations of itraconazole- (*comparative trough, steady state plasma itraconazole concentrations of SUBA-itraconazole 65mg capsules with food to itraconazole 100mg capsules with food over 42 days)*
3. Efficacy: clinical outcomes (time to relief of fungal signs and symptoms) at days 14, 28, and 42
4. Safety- defined as: adverse events that occurred in each study arm by Day 42
5. Tolerability - ability to remain on study drug at Days 14 & 28
6. Days of Hospitalization and ICU stays at Day 42
7. Other health economic endpoints:
    1. Number of unscheduled procedures (i.e., labs, scans, etc.) at Day 42
    2. Total number of capsules taken at Day 42
    3. SF-20 (QOL) assessments at Day 42

Stage II- Open-Label, Extension

Primary Endpoint

1. Efficacy- Free from proven or probable invasive endemic fungal infection at Day 180
2. Tolerability- ability to stay on study drugs at Days 43 - 180.

Secondary Endpoints

1. Safety- Adverse events that occurred in each study arm between Days 43 - 180 or end of therapy
2. Days of Hospitalization (Days 1 - 180) defined as days of hospitalization and ICU stays from randomization to Day 180 or end of therapy)

10.4 Data Review Committee

In addition to discrete laboratory parameters for PK, laboratory reports, days of hospitalization, ER and ICU stays, and safety reports; a data review committee (DRC) consisting of a DRC chair and 3 additional mycology experts will review data to determine safety and efficacy parameters as follows:

DRC-Assessments of Clinical Response (Baseline, Days 14, 28, 42, 84, 180)

Outcome	DRC-Assessed Clinical Response
Success	• Resolution of all attributable clinical symptoms, physical findings and radiography • Partial resolution of attributable clinical symptoms, physical findings and/or radiography
Failure	• No resolution and/or worsening of attributable clinical symptoms, physical findings, and/or radiography
Not applicable	• No attributable signs and symptoms present at baseline and no symptoms attributable to IFD developed post-baseline

DRC-Assessments of Mycological Response (Days Baseline, Days 14, 28, 42, 84, 180)

Outcome	DRC-Assessed Mycological Response
Success	• Eradication • Presumed eradication
Failure	• Persistence • Presumed persistence
Not applicable	• No mycological evidence available at baseline

10.5 Safety Review

A comparison of adverse events reported per study arm will be quantified and compared.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in this study, each site will permit authorized representatives of the sponsor(s), MSG, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated what data will be collected on CRFs and what data will be collected from other sources. ECRFs must be completed in their entirety regardless of the site's use of alternate source documents.

Refer to: (http://www.fda.gov/downloads/Drugs/Guidance/ucm073122.pdf).

12 QUALITY CONTROL AND QUALITY ASSURANCE

This section will address the plans for local quality assurance and quality control. (http://www.fda.gov/downloads/Drugs/Guidance/ucm073122.pdf).

All sites conducting research are required to have a plan in place for assuring the quality of the research being conducted.

Each site should have standard operating procedures (SOPs) for quality management which describe:

- How data will be evaluated for compliance with the protocol and for accuracy in relation to source documents.
- The documents to be reviewed (e.g., informed consents, eCRFs, clinic notes, product accountability), who is responsible, and the frequency for reviews should be identified, either in a formal quality management plan or in site SOPs.
- Methods of training for staff should be specified.

Additional information about site quality control are found in the Manual of Procedures

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

If the study is conducted at international sites, compliance with the Declaration of Helsinki, CIOMS, and International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), or another country's ethical policy statement, whichever provides the most protection to human subjects.

13.2 Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate independent ethics committee (IEC) or IRB. Any amendments to the protocol or consent materials must also be approved before they are placed into use.

13.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product. Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A model informed consent form for subject participation is provided in the Manual of Procedures. Each institution should place the informed consent document in its own template. Each institution may add but not remove anything from the model consent form.

13.4 Exclusion of Women, Minorities, and Children (Special Populations)

Study participants will consist of males or females, age 18 or greater, who meet eligibility requirements. Women who are pregnant will be excluded from participation because of potential side effects of the study drugs on the fetus. There are no exclusion criteria based on race or ethnicity.

13.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Management Responsibilities

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained.

The MSG Coordinating Center and/or its designee will provide guidance to investigators on making corrections to the source documents and eCRF.

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff at the site, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality, and reviewed by the site PI or designee.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. During the study, the investigator must maintain complete and accurate documentation for the study.

The MSGERC Statistical and Data Coordinating Center for this study will be responsible for data management, quality review, analysis, and reporting of the study data under the direction of the study statistician.

14.2 Data Capture Methods

Clinical data (including AEs, concomitant medications, and clinical assessments) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant Internet Data Entry System (IDES) provided by The MSG Statistical and Data Coordinating Center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.3 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedure's requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- Quality Assurance and Quality Control, section 5.1.1
- Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the MSG Coordinating Center by Email or fax.

All deviations from the protocol must be addressed in study subject source documents. A completed copy of the MSG Protocol Deviation Form must be maintained in the regulatory file, as well as in the subject's source document. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB/IEC requirements.

15 PUBLICATION POLICY

Following completion of the study, the investigator is expected to publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. **The MSG Coordinating Center will register this study in ClinicalTrials.gov.** Any clinical trial starting enrollment after 01 July 2005 must be registered on or before patient enrollment. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by 13 September 2005, before considering the results of the trial for publication.

The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., Phase I trials), would be exempt from this policy.

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APPENDIX A: SCHEDULE OF EVENTS

Activities	Day 1[g] (Baseline)	Day 7 (1 wk) +/- 3 days	Day 14 (2 wks) +/- 3 days	Day 28 (4wks) +/- 7 days	Day 42 (6 wks) +/- 3 days	Day 84 (3 mos) +/- 7 days	Day 180 (6 mos) +/- 7 days
Informed Consent	X						
Review of Inclusion/Exclusion Criteria	X						
Randomization	X						
Medical History	X						
Clinical Assessment: *vital signs, PE*[a]*, & radiographs*[b];	X	X	X	X	X	X	X
Participant Administered SF-12 Quality of Life Survey	X				X		X
Tolerability	X			X	X		X
βHCG - pregnancy test[c]	X						
Mycologic Assessment: clinical, *urine and serum quantitative antigen levels*[d] *& serum antibodies*[e,f]	X		X	X	X	X	X
Serum and Urine for future use: *blood, urine, saliva, sputum*[e]	X		X	X	X	X	X
Plasma PK[f]		X	X		X		
Chemistry: Creatinine, *AST and Alkaline Phosphatase, Total Bilirubin*[f]	X		X	X	X	X	X
Hematology: *CBC with Differential*[f]	X			X		X	X
HIV Status: Documentation of any positive test; Documentation of Negative test 30 days or less prior to start of study drug.	X						
Antifungal Therapy (Pre- and during study)	X	X	X	X	X	X	X
Dose Modifications			X	X	X	X	
Study Drug Dosing & Accountability	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Days of Hospitalization, ICU	X	X	X	X	X	X	X

[a] *Complete physical exam on baseline; targeted physical exams for all other visits.*

[b] *Radiograph results that were performed as standard of care to diagnose or assess the fungal infection.*

[c] *Urine or Serum pregnancy test is acceptable.*

[d] *Histoplasma and Coccidioides urine and serum quantitative antigen.*

[e] *Collection of sputum, if associated with the IFI and available.*

[f] *Chemistry and hematology will be processed at the site for safety evaluations; PK samples will be sent to a central lab for processing; see Manual of Procedures for specimen handling procedures;*

[g] *Baseline Visit: Study drug is be started on Day 1. Visit windows for Day 7, 14 and 42 will be a +/-3 day window. All other visits have a +/- 7 day window.*