

A Randomized, Double-blind, Placebo-controlled Clinical Trial of Fluconazole as Early Empiric Treatment of Coccidioidomycosis Pneumonia (Valley Fever) in Adults Presenting with Community Acquired Pneumonia (CAP) in Endemic Areas (FLEET-Valley Fever)

DMID Protocol Number: 14-0053

DMID Funding Mechanism: Vaccine and Treatment Evaluations Units

Lead Principal Investigator: Susanna Naggie, M.D., M.H.S. and Emmanuel Walter, M.D., M.P.H.

DMID Clinical Project Manager: Maureen Mehigan, R.N.

DMID Scientific Lead: Lanling Zou, M.D., Ph.D.

DMID Medical Officer: Varduhi Ghazaryan, M.D., M.P.H.

DMID Medical Monitor: Venus Shahamatdar, M.D.

Draft or Version Number: Version 5.0

29 Mar 2018

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) and as required by the following:

- United States Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312);
- International Conference on Harmonisation: Good Clinical Practice (ICH E6); 62 Federal Register 25691 (1997); and future revisions
- The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule-Final Modification (45 CFR Parts 160 and 164)
- National Institutes of Health (NIH) Office of Extramural Research, Research Involving Human Subjects, as applicable
- National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award, as applicable
- Applicable Federal, State, and Local Regulations and Guidance

Compliance with these standards provides public assurance that the rights, safety and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

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 provides the necessary assurance 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 E6 Good Clinical Practice (GCP) guidelines.

I agree to conduct the study in compliance with GCP and applicable regulatory requirements.

I agree to conduct the study in accordance with the current protocol and will not make changes to the protocol without obtaining the sponsor's approval and IRB/IEC approval, except when necessary to protect the safety, rights, or welfare of subjects.

Site Investigator Signature:

Signed: _____ Date: _____
Name
Title

Signed: _____ Date: _____
Name
Title

TABLE OF CONTENTS

STATEMENT OF COMPLIANCE.....	2
SIGNATURE PAGE	3
TABLE OF CONTENTS.....	4
LIST OF TABLES.....	9
LIST OF FIGURES	10
LIST OF ABBREVIATIONS.....	11
PROTOCOL SUMMARY	13
1. KEY ROLES	18
2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE	21
2.1. Background Information.....	21
2.2. Rationale	22
2.3. Potential Risks and Benefits	24
2.3.1. Potential Risks	24
2.3.2. Known Potential Benefits.....	26
3. OBJECTIVES AND OUTCOME MEASURES	27
3.1. Study Objectives.....	27
3.1.1. Primary	27
3.1.2. Secondary	27
3.1.3. Exploratory	27
3.2. Study Outcome Measures.....	28
3.2.1. Primary	28
3.2.2. Secondary	31
3.2.3. Exploratory	32
4. STUDY DESIGN	36
4.1. Sub-studies.....	37
5. STUDY ENROLLMENT AND WITHDRAWAL	38
5.1. Subject Inclusion Criteria	38
5.2. Subject Exclusion Criteria.....	39

5.3.	Treatment Assignment Procedures	40
5.3.1.	Randomization Procedures	40
5.3.2.	Masking Procedures.....	41
5.3.3.	Reasons for Withdrawal and Discontinuation of Study Product Administration	42
5.3.4.	Handling of Withdrawals and Discontinuation of Administration.....	43
5.3.5.	Subject Replacement	44
5.3.6.	Termination of Study.....	44
6.	STUDY INTERVENTION/INVESTIGATIONAL PRODUCT	45
6.1.	Study Product Description.....	45
6.1.1.	Acquisition.....	45
6.1.2.	Formulation, Packaging, and Labeling.....	45
6.1.3.	Product Storage and Stability	46
6.2.	Dosage, Preparation and Administration of Study Intervention/Investigational Product	46
6.3.	Modification of Study Intervention/Investigational Product for a Subject	46
6.4.	Accountability Procedures for the Study Intervention/Investigational Product(s).....	46
6.5.	Assessment of Subject Compliance with Study Intervention/Investigational Product/Investigational Device.....	47
6.6.	Concomitant Medications/Treatments.....	47
6.6.1.	Contraindicated medications	48
6.6.2.	Drug Interactions with Fluconazole.....	49
6.7.	Rescue Procedures	50
7.	STUDY SCHEDULE	51
7.1.	Pre-Screening Assessment [Optional] (occurring up to 72 hours prior to enrollment.....	51
7.2.	Screening/Enrollment/Baseline (Day 1, Visit 01)	52
7.3.	Follow-up (Days 22-180, Visits 02-07).....	54
7.3.1.	Follow-up Visit Visit 02 (Day 22):.....	54
7.3.2.	Follow-up Visit 03 (Day 29).....	56

7.3.3.	Follow-up Visit 04 (Day 43).....	57
7.3.4.	Follow-up Visit 05 (Day 49) – Telephone follow-up for those subjects randomized to Fluconazole only:.....	59
7.3.5.	Follow-up Visit 06 (Day 90): Telephone Follow-up for Coccidioidomycosis Positive Subjects Only.....	60
7.3.6.	Follow-up Visit 07 (Day 180): Telephone Follow-up for Coccidioidomycosis Positive Subjects Only	60
7.4.	Early Termination Visit (if needed).....	61
7.4.1.	Before Follow-up Visit 04.....	61
7.4.2.	After Follow-up Visit 04	62
7.5.	Unscheduled Visit.....	62
8.	STUDY PROCEDURES/EVALUATIONS.....	64
8.1.	Clinical Evaluations.....	64
8.2.	Laboratory Evaluations.....	66
8.2.1.	Clinical Laboratory Evaluations	66
8.2.2.	Special Assays or Procedures	66
8.2.3.	Specimen Preparation, Handling, and Shipping	67
9.	ASSESSMENT OF SAFETY	69
9.1.	Specification of Safety Parameters	69
9.2.	Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters.....	69
9.2.1.	Adverse Events	69
9.2.2.	Serious Adverse Events	70
9.2.3.	Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings	71
9.3.	Reporting Procedures.....	72
9.3.1.	Serious Adverse Events	72
9.3.2.	Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND.....	72
9.3.3.	Reporting of Pregnancy	73
9.4.	Type and Duration of Follow-up of Subjects after Adverse Events.....	73
9.5.	Halting Rules	73

9.6.	Safety Oversight (ISM plus SMC or DSMB).....	74
9.6.1.	Independent Safety Monitor (ISM)	74
9.6.2.	Data and Safety Monitoring Board (DSMB).....	74
10.	CLINICAL MONITORING	76
11.	STATISTICAL CONSIDERATIONS	77
11.1.	Study Hypotheses	77
11.2.	Sample Size Considerations	78
11.2.1.	Sample Size for Per Protocol Analysis Population.....	78
11.2.2.	Sensitivity of Sample Size to Assumptions	79
11.2.3.	Calculation of Target Enrollment	80
11.3.	Planned Interim Analyses	80
11.3.1.	Interim Safety Review	81
11.3.2.	Interim Immunogenicity or Efficacy Review	81
11.3.3.	Enrollment Feasibility	83
11.4.	Final Analysis Plan	85
11.4.1.	Analysis Populations	85
11.4.2.	Baseline Characteristics	86
11.4.3.	Safety Analysis Plan	86
11.4.4.	Efficacy Analysis Plan.....	87
12.	SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS	91
13.	QUALITY CONTROL AND QUALITY ASSURANCE	92
14.	ETHICS/PROTECTION OF HUMAN SUBJECTS	93
14.1.	Ethical Standard.....	93
14.2.	Institutional Review Board	93
14.3.	Informed Consent Process	94
14.3.1.	Informed Consent/Assent Process (in Case of a Minor)	95
14.4.	Exclusion of Women, Minorities, and Children (Special Populations).....	95
14.5.	Subject Confidentiality	95
14.6.	Study Discontinuation	96

14.7.	Costs, Subject Compensation, and Research Related Injuries	96
14.8.	Future Use of Stored Specimens and Data	96
14.9.	Permission to Be Contacted for Future Studies	97
15.	DATA HANDLING AND RECORD KEEPING	98
15.1.	Data Management Responsibilities	98
15.2.	Data Capture Methods	98
15.3.	Types of Data.....	98
15.4.	Timing/Reports	98
15.5.	Study Records Retention	98
15.6.	Protocol Deviations	99
16.	PUBLICATION POLICY	100
17.	LITERATURE REFERENCES.....	101
18.	SUPPLEMENTS/APPENDICES	103
APPENDIX A. SCHEDULE OF EVENTS.....		104

LIST OF TABLES

Table 1: Treatment Arms	16
Table 2: Modified Scoring System for Evaluating Treatment Response in Early Coccidioidal Pneumonia (FLEET CAP Score)*	29
Table 3: Extra-Pulmonary Symptom Score	33
Table 4: Case Definition 2 (Alternative Case Definition for Exploratory Analyses).....	34
Table 5: Power of the Z Test for Different Day 22 Response Rates	79
Table 6: Planned Interim Analysis Table.....	80
Table 7: Power of the Z Test for Different Day 22 Response Rates with a Futility Analysis	82
Table 8: Chance of Futility at Second Interim Analysis.....	82
Table 9: Chance of Futility at Third Interim Analysis.....	83
Table 10: Operating Characteristics of a Trial Design with Both a Futility and Sample Size Assessment at the Three Interim Analyses	84
Table 11: Secondary Efficacy Analyses	88
Table 12: Schedule of Study Procedures and Evaluations.....	104

LIST OF FIGURES

Figure 1: Schematic of Study Design.....	17
Figure 2: Geographic distribution of Endemic Coccidioidomycosis.....	22

LIST OF ABBREVIATIONS

ADHS	Arizona Department of Health Services
AE	Adverse Event/Adverse Experience
ARUP	Associated Regional and University Pathologist Inc.
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CAP	Community Acquired Pneumonia
CAR	Clinical Agents Repository
CDC	Centers for Disease Control and Prevention
CDPH	California Department of Public Health
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CPT	Current Procedural Terminology
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EIA	Enzyme Immunoassay
EO	Exploratory Objective
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDCF	Immunodiffusion Complement Fixation
IDE	Investigational Device Exemption

IDTP	Immunodiffusion Tube Precipitin
IEC	Independent or Institutional Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intent to Treat
JAMA	Journal of the American Medical Association
MedDRA [®]	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
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
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
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
PP	Per Protocol
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SDCC	Statistical and Data Coordinating Center
SF-12	Short Form-12
SO	Secondary Objective
SOP	Standard Operating Procedure
SpO ₂	Peripheral capillary oxygen saturation
TdP	Torsades de Pointes
US	United States
WHO	World Health Organization

PROTOCOL SUMMARY

Title:	A Randomized, Double-blind, Placebo-controlled Clinical Trial of Fluconazole as Early Empiric Treatment of Coccidioidomycosis Pneumonia (Valley Fever) in Adults Presenting with Community Acquired Pneumonia (CAP) in Endemic Areas (FLEET-Valley Fever)
Phase:	4
Population:	Up to 1000 adults aged 18 and older diagnosed with community acquired pneumonia whose health care provider has made the decision to treat
Number of Sites:	Vaccine and Treatment Evaluation Unit (VTEU) site or subcontract site and up to 25 community locations
Study Duration:	Approximately 72 months
Subject Participation	
Duration:	From 42 days to approximately 6 months
Description of Agent or Intervention:	Fluconazole: 400 mg (2 x 200 mg tablets) in over-encapsulated tablets Placebo: Matched for size, shape, and color
Objectives:	Primary: <ul style="list-style-type: none">• To assess the clinical response of early empiric antifungal therapy with fluconazole at Day 22 in subjects with coccidioidomycosis pneumonia who are adherent to the study intervention. Secondary: <ul style="list-style-type: none">• To assess the clinical response of early empiric antifungal therapy with fluconazole at Day 22 in subjects with coccidioidomycosis pneumonia regardless of adherence with the study intervention.• To assess the clinical response of early empiric antifungal therapy with fluconazole at Day 43 in subjects with

coccidioidomycosis pneumonia regardless of adherence with the study intervention.

- To compare the clinical response and its individual components over time, by treatment group, in subjects with coccidioidomycosis pneumonia.
- To assess the impact of early empiric antifungal therapy with fluconazole on days lost from work or school and responses to the SF-12v2 and PROMIS Item Bank v2.0 - Ability to Participate in Social Roles and Activities - Short Form 4a in subjects with coccidioidomycosis pneumonia.
- To assess the effect of early empiric antifungal therapy with fluconazole through Day 43 in subjects with coccidioidomycosis pneumonia on all-cause mortality by treatment group.
- To assess whether early empiric antifungal therapy with fluconazole at Day 22 is non-inferior to placebo as defined by clinical response at Day 22 in all randomized subjects, regardless of coccidioidomycosis pneumonia status or adherence with study intervention, with baseline and follow-up FLEET-CAP scores.

Exploratory:

- To assess the effect of early empiric fluconazole therapy on the immune response to coccidioidomycosis in subjects with suspected coccidioidomycosis pneumonia.
- To assess the effect of early empiric fluconazole therapy on the development of extrapulmonary symptoms associated with coccidioidomycosis pneumonia.
- To assess the effects of early empiric fluconazole therapy on the occurrence of disseminated coccidioidomycosis in subjects with pneumonia in coccidioidomycosis-endemic areas.
- To characterize the natural history of coccidioidomycosis disease by examining the clinical response and its individual

components over time, in placebo recipients with coccidioidomycosis pneumonia.

- To assess the clinical response of early empiric antifungal therapy with fluconazole at Day 22 in subjects with coccidioidomycosis pneumonia based on an alternative serologic case definition for coccidioidomycosis pneumonia.
- To compare the clinical signs and symptoms of community-acquired pneumonia caused by coccidioidomycosis pneumonia with the clinical signs and symptoms caused by non-coccidioidomycosis pneumonia in coccidioidomycosis-endemic areas.
- To characterize the safety of early empiric antifungal therapy with fluconazole with respect to liver function in subjects with pneumonia in coccidioidomycosis- endemic areas.
- To assess the adherence to long term self-administration of daily fluconazole or placebo in a clinical trial setting using self-reported adherence and pill count.
- To assess medication adherence in the active fluconazole arm by measuring fluconazole levels.

Outcome Measures:

Primary:

- See Protocol Section 3.2

Secondary:

- See Protocol Section 3.2

Exploratory (*if applicable*):

- See Protocol Section 3.2

Description of Study Design:

This is a Phase IV randomized, double-blinded, placebo-controlled study in 1000 individuals aged 18 years or older, with community acquired pneumonia (CAP) who meet all eligibility criteria in *Coccidioides* endemic regions. This study is designed to provide data on the efficacy of early empiric antifungal

treatment (fluconazole, 400 mg/day) for coccidioidomycosis pneumonia (also referred to as Valley Fever (VF) Pneumonia or acute onset valley fever). The hypothesis is that early empiric treatment with fluconazole in highly endemic regions is effective in reducing the frequency, severity and associated adverse outcomes of infection with recently acquired coccidioidomycosis pneumonia.

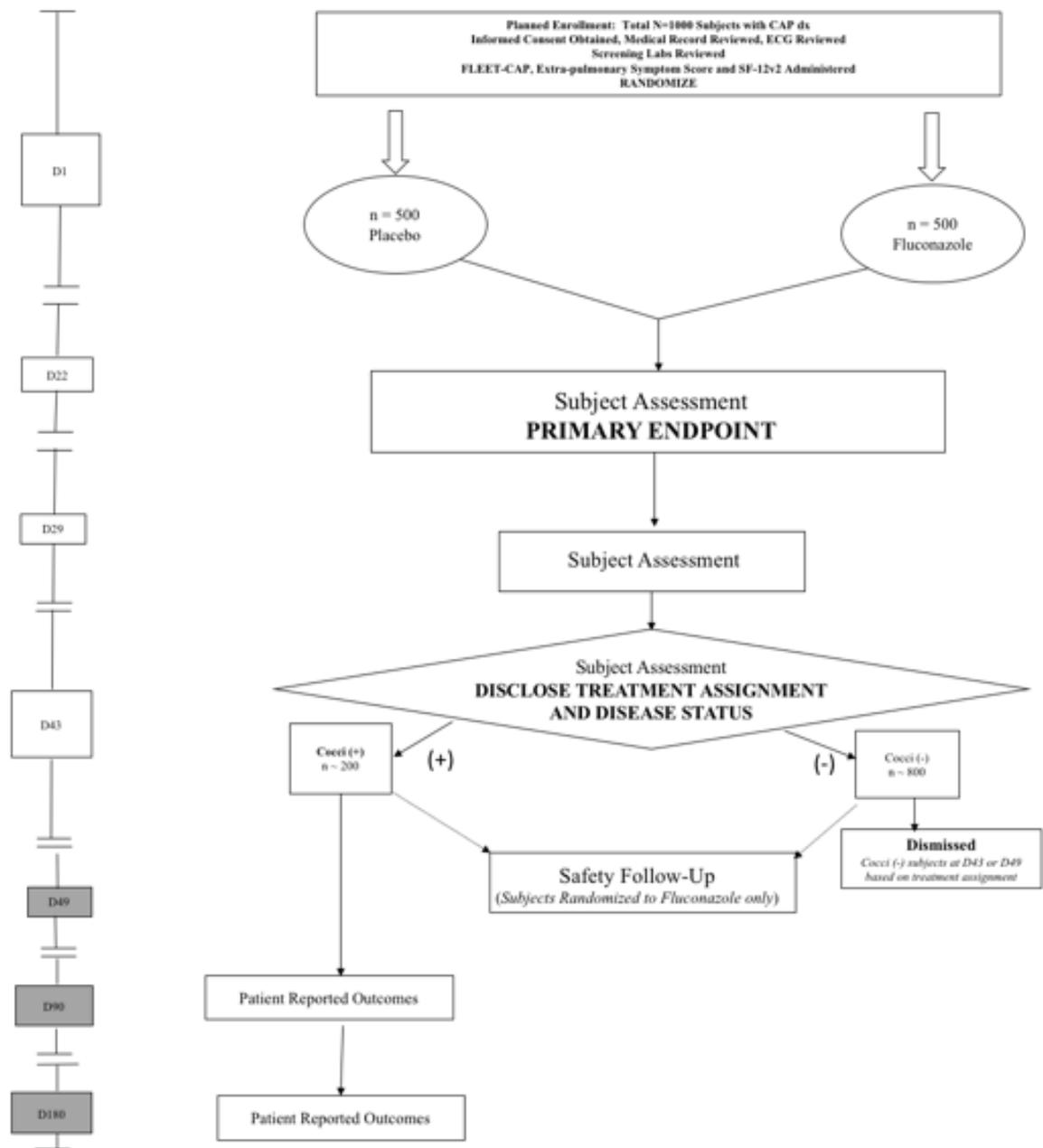
Individuals with CAP, who are determined by their healthcare provider to require antibacterial therapy, will be randomized to receive either standard CAP treatment (as determined by provider) plus placebo (Group 1) or standard CAP treatment (as determined by provider) plus 400 mg/day of fluconazole (Group 2) for 42 days.

Estimated Time to Complete Enrollment: Approximately 60 months

Table 1: Treatment Arms

Cohort A	ARM 1	500	Fluconazole
	ARM 2	500	Placebo

Figure 1: Schematic of Study Design



1. KEY ROLES

Individuals:

Site Principal Investigator: Susanna Naggie, M.D., M.H.S.
Duke Clinical Research Institute
2400 Pratt Street, Room 0311 Terrace Level
Durham, NC 27705
Phone: 919-684-2584
Fax: 919-668-7164
Email: susanna.naggie@duke.edu

Emmanuel Walter, M.D., M.P.H.
Duke Clinical Vaccine Unit
2608 Erwin Road Suite 210
Durham, NC 27705
Phone: 919-620-5346
Fax: 919- 613-1559
Email: walte002@mc.duke.edu

Maureen Mehigan, R.N.
5601 Fishers Lane, 7E19, MSC 9826
Bethesda, MD 20892-9826
For courier service use Rockville, MD 20852
Phone: (240) 627-3317
Email: mmehigan@niaid.nih.gov

DMID

Clinical Project Manager:

DMID Scientific Lead: Lanling Zou, M.D., Ph.D.
5601 Fishers Lane, Room 7E21 MSC 9826
Bethesda, MD 20892
Phone: 240-627-3400
Email: lanlingz@niaid.nih.gov

DMID Medical Officer Carmelle T. Norice-Tra, MD-PhD

5601 Fishers Lane, 7E36
Bethesda, Maryland 20892
For courier service use Rockville, MD 20852
Direct Phone: 301-761-5433
Cell Phone: 301-325-5343
Branch Fax: 301-402-2508
Email: carmelle.norice@nih.gov

DMID Medical Monitor

Venus Shahamatdar, M.D.
5601 Fishers Lane, 7E54 MSC 9826
Bethesda, Maryland 20892-9826
For courier service use Rockville, MD 20852
Phone: 240-627-3369
Email: venus.shahamatdar@nih.gov

Institutions:

Duke University
2608 Erwin Road, Ste 210
Durham, NC 27705
Emmanuel Walter, MD, MPH
919-620-5346
chip.walter@duke.edu

**Safety and
Pharmacovigilance
Contractor:**

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support
(CROMS)
6500 Rock Spring Dr., Suite 650
Bethesda, MD 20817
SAE Hot Line: 1-800-537-9979 (US)
SAE Fax: 800-275-7619 (US)

SAE Email: PVG@dmidcroms.com

Data Coordinating Center: The Emmes Corporation
401 N Washington Street
Suite 700
Rockville, MD 20850
Phone: (301) 251-1161
Fax: (301) 251-1355
Email: valleyfever@emmes.com

Study Agent Repository: Fisher BioServices
Thermo Fisher Scientific
20439 Seneca Meadows Parkway
Germantown, MD 20876
Christine Demasco-Cody
Phone: (240) 477-1357
Fax; (240) 477-1360
Email: Christine.demasco-cody@thermofisher.com

Laboratory(ies), if applicable: ARUP Laboratories
500 Chipeta Way
Salt Lake City, Utah 84108-1221
Phone: (801) 583-2787
Fax: (801) 583-2712
Email: www.aruplab.com

UC-Davis
Department of Medical Microbiology and Immunology
1 Shields Avenue, Tupper Hall, Rm. 3146
Davis, CA 95616
George R. Thompson, MD, FIDSA
Phone: (530) 752-3545
Fax: (530) 752-5692
Email: grthompson@ucdavis.edu

2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

Coccidioidomycosis is caused by the dimorphic fungal pathogens *Coccidioides posadasii* and *Coccidioides immitis* which primarily live in soil. These infections occur almost exclusively in the Southwestern part of the United States, primarily in areas of low rainfall, high summer temperatures and moderate winter temperatures, with more than 70% of reported cases occurring in Arizona and the majority of remaining cases found in parts of southern California (Figure 1). In affected areas, coccidioidomycosis is estimated to cause 15% to 29% of all community acquired pneumonia with an estimated risk of infection of 3% per year among coccidioidomycosis pneumonia-naïve persons [1]. Infection occurs after inhalation of fungal spores aerosolized from the soil, where the fungus resides as mycelial form. In 2011, there were over 20,000 reported cases of coccidioidomycosis and an estimated 150,000 additional cases went undiagnosed [2].

The Centers for Disease Control and Prevention (CDC) Mycotic Diseases Branch worked with Arizona Department of Health Services (ADHS) and California Department of Public Health (CDPH) to identify public and private healthcare facility networks in Phoenix and Tucson, AZ and Bakersfield, CA that could support the volume of pneumonia patients diagnosed in an outpatient setting and reported the number of coccidioidomycosis patients needed to run this randomized controlled trial (RCT). For purposes of this data collection, CDC defined CAP as a patient with an ICD-9 code for pneumonia of unspecified etiology (480.9, 482.9, 485, or 486) as a primary or secondary diagnosis. Additionally facilities were asked to restrict pneumonia diagnosed patients to those with a current procedural terminology (CPT) code for chest radiography within 2 weeks prior to and 4 weeks following the first encounter when one of the ICD-09 codes was assigned. Restriction to patients with chest radiography was not possible at all facilities. Testing for coccidioidomycosis was defined as use of a CPT code for a serology test (86635) within 2 months following the incident pneumonia visit. A positive coccidioidomycosis test was defined as serum serology obtained within 2 months of the CAP diagnosis and reported as positive to the ADHS or CDPH database.

Cumulatively, these facilities diagnosed 5,008 cases of CAP in outpatient setting (including primary care outpatient facilities, urgent care facilities, and emergency departments) in 2012. Of these cases, 896 (18%) were known to be tested for coccidioidomycosis, although the proportion tested varied ranged 5% to 39% by facility. Overall, of CAP cases known to be tested, 178 (20%) were reported as coccidioidomycosis positive to respective health department, however, this proportion varied from 7% to 45% by facility, and even various clinic types within the facility. In

general, a smaller proportion of CAP cases seen at emergency departments tested positive for coccidioidomycosis as compared with cases seen at other facility types.

Figure 2: Geographic distribution of Endemic Coccidioidomycosis



<http://www.cdc.gov/fungal/diseases/coccidioidomycosis/>

2.2. Rationale

The presentation of coccidioidomycosis pneumonia ranges from a non-specific and self-limited febrile illness to primary pulmonary pneumonia and more systemic dissemination including meningitis. A significant proportion of patients diagnosed with primary pulmonary coccidioidomycosis will experience a protracted disease course with prolonged symptoms and median time to complete symptom resolution of approximately 18 weeks [3]. Up to 82% of patients with primary pulmonary coccidioidomycosis missed work due to their illness in one prospective cohort study. To complicate the diversity of clinical manifestations, there is also a paucity of effective diagnostic tests to establish a clinical diagnosis early in the course of infection. The sensitivity and specificity of currently available diagnostic tests are not sufficient.

In addition, it is not fully understood whether a single diagnostic test is sufficient to identify and/or differentiate the different presentations and stages (acute vs. chronic, primary vs. disseminated) of coccidioidomycosis. As such, antifungal treatment is often delayed and initiated after those with community acquired pneumonia (CAP) fail to respond to antibacterial therapies. In 2013, total in-patient charges for Arizona residents hospitalized with the primary diagnosis of Coccidioidomycosis approached \$53 million, with a median \$40,321 per hospitalization [4]. About 40% of diagnosed coccidioidomycosis cases are hospitalized at a cost of almost \$50,000 per visit [5]. As population and travel to endemic areas increases, so will the risk of potential infection and the total costs of providing care to subjects who are infected. It is therefore necessary to find an effective means of reducing the severity and duration of this disease. This clinical trial hopes to rectify the current lack of a decisive treatment paradigm in communities with a high incidence of coccidioidomycosis.

The diagnosis of coccidioidomycosis is usually considered after a patient does not respond to conventional antibacterial treatment for CAP. This means that antifungal treatment is often delayed. The consideration of coccidioidomycosis only after failure of antibacterial therapy for CAP and the lack of timely diagnosis make it difficult for clinical trials to come to definitive conclusions; therefore, there are no evidence-based, decisive treatment protocols (or guidelines) for the treatment of coccidioidomycosis.

This trial, therefore, seeks to enroll patients in endemic areas with CAP (wherein viral and bacterial etiologies predominate) who are prescribed antibacterials by their health care provider (clinic, urgent care facility or emergency department) upon their initial visit, in order to compare the efficacy of early empiric anti-fungal treatment (fluconazole) in patients for whom a coccidioidomycosis diagnosis is possible, though not yet confirmed. [6].

Such a design provides several advantages. Administration of an antifungal agent will enable the effect evaluation of the potential benefit of early administration of antifungal treatment. This design also limits the risk to participants, since standard of care antibacterials will be prescribed to all enrolled subjects by their treating health care provider. Additionally, all participants who are diagnosed with coccidioidomycosis during the study period will be referred to a health care provider for assessment and determination of need to initiate, continue or cease treatment at the time their status is revealed. All subjects who meet the protocol defined case definition for coccidioidomycosis will be followed for a total of 6 months. Those subjects originally randomized to the placebo arm will be referred to a health care provider for consideration of coccidioidomycosis treatment at Day 43. This potential delay in treatment is no longer than the usual delay in treatment in current clinical practice, due to the fact that diagnosis is usually based on non-response to a first course of antibacterial and serologic evidence of coccidioidomycosis. Subjects who are randomized to fluconazole but are ultimately determined to be

coccidioidomycosis-negative will be followed after their status is revealed to monitor for treatment side effects.

2.3. Potential Risks and Benefits

2.3.1. Potential Risks

The potential risks of this study are those associated with having blood drawn, possible reactions to the fluconazole treatment and breach of confidentiality.

Most individuals who enroll in this study will not be infected with coccidioidomycosis and will not have a condition known as Valley Fever Pneumonia. Therefore, many of the individuals in the active treatment arm will be receiving an antifungal agent even though they have no fungal infection. Fluconazole will be dosed to treat coccidioidomycosis pneumonia based on existing Infectious Diseases Society of America (IDSA) recommendations for the treatment of non-meningeal infections in non-immunocompromised hosts. The treatment of coccidioidomycosis with fluconazole is not a listed indication on the package insert.

Fluconazole: Fluconazole has a well described safety profile and well defined adverse reactions that include: headaches (13%), nausea (7%), abdominal pain (6%), diarrhea (up to 3%). In less than 1% of individuals taking this medication there is a perversion of taste. Other less common side effects may include: serious liver damage, including death (signs include dark urine, light-colored stools, vomiting, or having severe skin itching), or an allergic reaction (signs include shortness of breath; coughing; wheezing; fever; chills; throbbing of the heart or ears; swelling of the eyelids, face, mouth, neck, or any other part of the body; or skin rash, hives, blisters or skin peeling). There are rare reports of exfoliative dermatitis, some of which were fatal. Individuals who have contraindications for treatment with fluconazole (e.g., allergy, intolerance, or contraindicated concomitant medications) will not be enrolled in the study. For patients who do not have coccidioidomycosis pneumonia but receive fluconazole, there is expected only a minimal increase in treatment-related risks.

In this study, the serological results for coccidioidomycosis conversion will not be disclosed until Day 43. While there are safeguards built in for subjects who clinically worsen (as described in Section 6.7), there is the potential for individuals who continue to feel poor or who clinically worsen to seek unnecessary/inappropriate additional antimicrobial treatment. We hope to reduce this risk by providing potential participants with information regarding this risk during the consent process. Furthermore, the clinical follow-up during the study will include assessments for symptom improvement and the site teams will be responsible for addressing any reports of clinical worsening as would be expected as part of standard of care.

There is no expected increased potential risk in delaying the treatment with fluconazole in patients who have coccidioidomycosis pneumonia and receive placebo, as there is usually a

delay in treatment because of the lack of diagnostic tests to establish a clinical diagnosis early in the course of infection.

Drug-drug interactions: The standard of care for management of CAP includes a macrolide- or fluoroquinolone-based regimen as first-line for outpatient management [7]. As such, there is a potential risk for clinically-significant drug-drug interactions when either antibacterial is used in combination with a triazole antifungal such as fluconazole. While azithromycin is known to be less arrhythmogenic than other macrolides including erythromycin and clarithromycin, large surveillance cohorts have demonstrated an increase in cardiovascular death among patients exposed to azithromycin, presumably related to QT prolongation and cardiac arrhythmias [8, 9]. Further, the combination of fluoroquinolones and triazoles (voriconazole or fluconazole) has been associated with clinically significant changes in QTc in up to 20% of patients in a hematologic malignancy cohort [10]. Fluconazole has been implicated in cases of torsades de pointes (TdP), most often occurring in patients at increased risk for TdP for other reasons, including sex (women), electrolyte abnormalities, concomitant medication administration or baseline cardiac dysfunction [11]. Potential subjects will undergo baseline 12-lead electrocardiogram (ECG) testing at Day 1 visit, and those patients who are deemed high-risk for development of TdP (based on baseline QTc, cardiac co-morbidities and/or concomitant anti-arrhythmic drugs or positive family history of long QT interval) will be excluded from the study.

Renal Clearance: In normal subjects, fluconazole is cleared primarily by renal excretion, with approximately 80% of the administered dose appearing in the urine as unchanged drug. About 11% of the dose is excreted in the urine as metabolites. The pharmacokinetics of fluconazole are markedly affected by reduction in renal function. There is an inverse relationship between the elimination half-life and creatinine clearance. Potential subjects with significantly impaired renal function (estimated CrCl < 50mL/min) will be excluded from participation to assure safety, given the need to dose-reduce fluconazole at this level of renal impairment.

Pregnancy: For approved indications, the fluconazole dosage used in this protocol is classified as category D risk for pregnant females. Category D risk indicates there is positive evidence of human fetal risk, including increased risk or rates of miscarriages, based on adverse reaction data from investigational or marketing experience or studies in humans. However, potential benefits may warrant use of the drug in pregnant women despite potential risks. A few published case reports describe a rare pattern of distinct congenital anomalies in human infants exposed in utero to doses between 400-800 mg/day of fluconazole. The risk benefit ratio for fluconazole when used in this protocol is still unknown, thus pregnant women will be excluded from participating in this study. In addition, pregnancy testing will be performed in all women of childbearing potential prior to randomization and throughout the duration of the study intervention. All women of childbearing potential will be required to use a highly effective method of birth

control. Any pregnancy will be cause for discontinuation of active treatment and will be followed for up to two months after birth to assess for potential adverse effects to the fetus.

Other unknown risks, discomforts, or side effects: There is a theoretical risk that early treatment may modify the host response and that treatment will impair host control and may lead to more relapses after treatment is eventually stopped.

Electrocardiogram (ECG): Mild skin irritation from the application and/or removal of the ECG patches is possible.

Blood sampling: Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the subject lie down. Bruising at the blood draw site may occur, but can be prevented or lessened by applying pressure to the draw site for several minutes.

Drawing blood may also cause infection. The use of aseptic technique will make infection at the site where blood will be drawn extremely unlikely.

Nasopharyngeal swab: Side effects of collecting a nasal pharyngeal swab may include mild discomfort and/or irritation of the nasal passage, occasional gagging, and rarely bleeding of the nasal passage.

Throat swab: Side effects of collecting a throat swab may include mild discomfort and/or irritation of the throat passage and occasional gagging.

Confidentiality: Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subjects' PHI. All paper records will be kept in a locked file cabinet or maintained in a locked room at the participating sites. Electronic files will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects by name. Organizations that may inspect and/or copy research records maintained at the participating sites for quality assurance and data analysis include groups such as National Institute of Allergy and Infectious Diseases (NIAID) or their designees and Food and Drug Administration (FDA).

2.3.2. Known Potential Benefits

One of the known potential benefits of this clinical trial is that all participants will have knowledge of their coccidioidomycosis serologic status. Additionally, there is potential that early empiric therapy may clinically help those who have coccidioidomycosis pneumonia by more promptly treating pneumonia and reducing associated clinical symptoms and long-term sequelae of pneumonia and possible dissemination of infection to other body sites.

3. OBJECTIVES AND OUTCOME MEASURES

3.1. Study Objectives

3.1.1. Primary

- To assess the clinical response of early empiric antifungal therapy with fluconazole at Day 22 in subjects with coccidioidomycosis pneumonia who are adherent to the study intervention.

3.1.2. Secondary

- To assess the clinical response of early empiric antifungal therapy with fluconazole at Day 22 in subjects with coccidioidomycosis pneumonia regardless of adherence with the study intervention.
- To assess the clinical response of early empiric antifungal therapy with fluconazole at Day 43 in subjects with coccidioidomycosis pneumonia regardless of adherence with the study intervention.
- To compare the clinical response and its individual components over time, by treatment group, in subjects with coccidioidomycosis pneumonia.
- To assess the impact of early empiric antifungal therapy with fluconazole on days lost from work or school and responses to the SF-12v2 and PROMIS Item Bank v2.0 - Ability to Participate in Social Roles and Activities - Short Form 4a in subjects with coccidioidomycosis pneumonia.
- To assess the effect of early empiric antifungal therapy with fluconazole through Day 43 in subjects with coccidioidomycosis pneumonia on all-cause mortality by treatment group.
- To assess whether early empiric antifungal therapy with fluconazole at Day 22 is non-inferior to placebo as defined by clinical response at Day 22 in all randomized subjects, regardless of coccidioidomycosis pneumonia status or adherence with study intervention, with baseline and follow-up FLEET-CAP scores.

3.1.3. Exploratory

- To assess the effect of early empiric fluconazole therapy on the immune response to coccidioidomycosis in subjects with suspected coccidioidomycosis pneumonia.
- To assess the effect of early empiric fluconazole therapy on the development of extrapulmonary symptoms associated with coccidioidomycosis pneumonia.

-
- To assess the effects of early empiric fluconazole therapy on the occurrence of disseminated coccidioidomycosis in subjects with pneumonia in coccidioidomycosis-endemic areas.
 - To characterize the natural history of coccidioidomycosis disease by examining the clinical response and its individual components over time, in placebo recipients with coccidioidomycosis pneumonia.
 - To assess the clinical response of early empiric antifungal therapy with fluconazole at Day 22 in subjects with coccidioidomycosis pneumonia based on an alternative serologic case definition for coccidioidomycosis pneumonia.
 - To compare the clinical signs and symptoms of community-acquired pneumonia caused by coccidioidomycosis pneumonia with the clinical signs and symptoms caused by non-coccidioidomycosis pneumonia in coccidioidomycosis-endemic areas.
 - To characterize the safety of early empiric antifungal therapy with fluconazole with respect to liver function in subjects with pneumonia in coccidioidomycosis-endemic areas.
 - To assess the adherence to long term self-administration of daily fluconazole or placebo in a clinical trial setting using self-reported adherence and pill count.
 - To assess medication adherence in the active fluconazole arm by measuring fluconazole levels.

3.2. Study Outcome Measures

3.2.1. Primary

- The proportion of subjects who achieve a clinical response at Day 22 in each treatment group.
 - “Clinical response” is defined as at least a 50% reduction in composite FLEET CAP score from baseline.

Efficacy outcome measures are based on a clinical scoring system that allows a constellation of clinical symptoms to be quantified and scored over time: cough, fatigue, chest pain, dyspnea, sputum production, night sweats, fever and hypoxia (see [Table 2](#)). The recall period for symptom assessments will be during the past week, with the exception of fever and hypoxia, which will be measured on the day the FLEET CAP is administered.

Table 2: Modified Scoring System for Evaluating Treatment Response in Early Coccidioidal Pneumonia (FLEET CAP Score)*

Community-Acquired Pneumonia (CAP) SYMPTOMS	Points	Proposed Definition
**Cough	0	No coughing, unaware of coughing or cough only now and then
	1	Occasional coughing (less than hourly)
	2	Frequent coughing (one or more times per hour), interferes with sleep
	3	Almost constant coughing (never free of cough or need to cough), makes sleep almost impossible
***Fatigue	0	Absent
	1	Minimal interference with physical function, no interference with carrying out duties and responsibilities
	2	Interference with carrying out duties and responsibilities
	3	Prevents usual work, school, family or social interactions
Chest pain	0	Absent
	1	Noticeable only when coughing
	2	Noticeable during deep breaths or when coughing
	3	Almost constant, present even when resting, without cough
**Dyspnea (Shortness of breath)	0	None, unaware of any difficulty
	1	Noticeable during strenuous activity
	2	Noticeable during light activity, or when washing or dressing
	3	Almost constant, present even when resting
**Sputum production	0	None, unaware of any difficulty or rarely caused problem
	1	Noticeable as a problem
	2	Causes a great deal of inconvenience
	3	An almost constant problem
Night sweats	0	Absent
	1	Bed clothing (e.g., pajamas) damp
	2	Bedding wet and requires change of bedding or clothing
Fever	0	Less than 37.8°Celsius
	1	37.8° – 38.5°Celsius
	2	38.6 – 39.5° Celsius
	3	Greater than 39.5° Celsius
Hypoxia	0	SpO₂ greater than or equal to 96% on Room Air
	1	96% > SpO₂ ≥89% on Room Air
	2	SpO₂ < 89% on Room Air
Total Score		

*An amalgam of multiple clinical scores [12-17].

**Modified from Breathlessness, Cough, and Sputum Scale (BCSS) [18].

***Modified from Fatigue Severity Scale (FSS) [19].

This primary analysis will be performed in the cocci-positive per-protocol population of subjects who meet the case definition of coccidioidomycosis pneumonia and who were adherent to the intervention administration (See Section 11.4.1). As defined below, adherence will be defined as taking at least 80% of the study medication (fluconazole or placebo) as determined at the day 22 visit. Pill count, if available, will take precedence over patient report of adherence.

Case Definition

The case definition of coccidioidomycosis pneumonia is met if the is subject diagnosed with CAP at the time of enrollment as determined by the referring health care provider, and meets one of the following serologic criteria:

1. The patient is positive for any two serologic tests at any time point from Day 1 through Day 29. The two positive results can but do not necessarily have to be from the same assay or the same time point. The assays considered for this criteria are: Immunodiffusion testing [IDTP (IgM) and IDCF (IgG)]; Enzyme linked immunoassay testing (EIA-IgM and EIA-IgG); OR
2. The patient is negative for anti-*Coccidioides* antibody by immunodiffusion assay (or EIA-IgG) at Day 1 and sero convert to positive for anti-*Coccidioides* antibody by immunodiffusion assay (or EIA-IgG) at any time point after Day 1 through Day 29; OR
3. The patient is negative or indeterminate for anti-*Coccidioides* antibody by CF assay on Day 1 and demonstrates a titer of greater than or equal to 2 by CF assay at any point after Day 1 through Day 29; OR
4. The patient is positive for anti-*Coccidioides* antibody by CF assay on Day 1 and demonstrates a rise of greater than or equal to 2-fold dilution in Complement Fixation (CF) titer compared to baseline at any time point after Day 1 through Day 29.

All serologic testing for a single participant from Day 1 through Day 29 will be batched and run concurrently to eliminate confounding due to test run variability.

Adherence

Adherence in all subjects will be assessed by patient self-report and pill count according to standard procedures, on Days 22, 29 and 43. Pill count, if available, will take precedence over patient report. If pill count is not available, patient report will be used.

To be considered adherent at a visit when the clinical response is measured, the subjects will need to have taken at least 80% of their expected pills.

Secondary analyses of the primary objective will be performed in multiple analysis populations (see Section 11.4.1).

3.2.2. Secondary

See Section 11.4.4.2 for a discussion of the analysis populations utilized for the secondary outcome measures.

Secondary Outcome 1:

- The proportion of subjects who achieve a clinical response at Day 22 in each treatment group, including in all randomized subjects who took at least one dose of study medication.
 - “Clinical response” is defined as at least a 50% reduction in composite FLEET CAP score from baseline.

Secondary Outcome 2:

- The proportion of subjects who achieve a clinical response at Day 43 in each treatment group, including in all randomized subjects who took at least one dose of study medication.
 - “Clinical response” is defined as at least a 50% reduction in composite FLEET CAP score from baseline. Note that a subject who responds earlier before Day 43 does not need to achieve a clinical response at Day 43, as well.

Secondary Outcome 3:

- The mean, median, and quartiles of the FLEET CAP score at Days 22, 29 and 43 in each treatment group.
- The mean, median, and quartiles for each component of the FLEET CAP score at Days 22, 29 and 43 in each treatment group.
 - Cough
 - Fatigue
 - Chest Pain
 - Dyspnea (Shortness of breath)
 - Sputum production
 - Night Sweats
 - Fever
 - Hypoxia

Secondary Outcome 4:

-
- Number of days of school or work missed due to illness after the start of the treatment through Day 43 in each treatment group.
 - The mean, median, and quartiles for the mental component summary (MCS) and physical component summary (PCS) scores of the SF-12v2 instrument and the responses to the individual items of the PROMIS Item Bank v2.0 - Ability to Participate in Social Roles and Activities - Short Form 4a at Days 22, 29, 43, 90 and 180 in each treatment group.

Secondary Outcome 5:

- Incidence rate of all-cause mortality after the start of treatment and through Day 43 by treatment group.
 - Mortality information will be obtained through medical records or next of kin.

Secondary Outcome 6:

- The proportion of subjects who achieve a clinical response at Day 22 among all randomized subjects, regardless of coccidioidomycosis status or adherence to study drug, in each treatment group.

3.2.3. Exploratory

Exploratory Outcome 1:

- The time to first detection of positive anti-Coccidioides antibodies, as measured through Day 43 in each treatment group.
 - The results of antibody determination in concurrent testing of serial specimens by the following assays will be evaluated: Complement fixation (CF); qualitative immunodiffusion with CF antigen (IDCF); qualitative immunodiffusion with tube precipitin antigen (IDTP), and quantitative IDCF.

Exploratory Outcome 2:

- The mean, median, and quartiles of a composite Extra-Pulmonary Symptom Score at Days 22, 29, 43, 90 and 180 among subjects with coccidioidomycosis pneumonia, in the absence of disseminated disease, in each treatment group.
- The mean, median, and quartiles for each component of an Extra-Pulmonary Symptom Score (see [Table 3](#)) at Days 22, 29, 43, 90 and 180 among subjects with coccidioidomycosis pneumonia, in the absence of disseminated disease, in each treatment group
 - Arthralgia
 - Rash
 - Headache

Table 3: Extra-Pulmonary Symptom Score

Extra-Pulmonary Symptom Score	Points	Proposed Definition
Arthralgia*	0	None
	1	Mild (scored ≤ 3 on visual analog scale)
	2	Moderate (scored 4-6 on visual analog scale)
	3	Severe (scored 7-10 on visual analog scale)
Rash	0	Absent
	1	Covers less than one arm or one leg
	2	Covers more than one arm or one leg but does not itch
	3	Covers more than one arm or one leg and itches
Headache*	0	None
	1	Mild (scored ≤ 3 on visual analog scale)
	2	Moderate (scored 4-6 on visual analog scale)
	3	Severe (scored 7-10 on visual analog scale)
Total Score		

* Measurements on the visual analog scale will be rounded to the nearest cm for the purposes of assigning a score, where five-tenths will be rounded up.

Exploratory Outcome 3:

- The time to diagnosis of disseminated coccidioidomycosis, as measured through Day 180 after the start of the study among subjects with coccidioidomycosis pneumonia in each treatment group.
 - The diagnosis of disseminated disease in a case of coccidioidomycosis is defined as a diagnostic code of disseminated coccidioidomycosis given to the subject between Days 1 and 180 by the subject’s health care provider as determined by medical record review on Day 180.

Exploratory Outcome 4:

- The mean, median, and quartiles for the composite clinical FLEET CAP score and each of its individual components at Days 22, 29 and 43 in placebo recipients with coccidioidomycosis pneumonia.
 - Cough
 - Fatigue

- Chest Pain
- Dyspnea (Shortness of breath)
- Sputum production
- Night Sweats
- Fever
- Hypoxia

Exploratory Outcome 5:

- Repeat the analysis of the Primary Objective, and secondary objectives 1-6 with the alternative serologic case definition (see [Table 4](#)).

Table 4: Case Definition 2 (Alternative Case Definition for Exploratory Analyses)

Patients who meet at least one of the following criteria are considered cases [#] :
Patient is negative for anti- <i>Coccidioides</i> antibody by complement fixation (CF) assay on Day 1, and demonstrates a titer of greater than or equal to 2 by CF assay at both Days 22 and Day 29
Patient is negative for anti- <i>Coccidioides</i> antibody by complement fixation (CF) assay on Day 1, and demonstrates a titer of greater than or equal to 4 by CF assay at either Day 22 or Day 29
Patient is negative for anti- <i>Coccidioides</i> antibody by immunodiffusion CF (IDCF, IgG) on Day 1, and has a positive IDCF test on either Day 22 or Day 29
Patient is negative for anti- <i>Coccidioides</i> antibody by immunodiffusion TP (IDTP, IgM) on Day 1, and has a positive IDTP test on either Day 22 or Day 29
Patient is negative for anti- <i>Coccidioides</i> antibody by enzyme linked immunoassay testing (EIA-IgM) on Day 1, and has positive EIA-IgM at both Days 22 and Day 29
Patient is negative for anti- <i>Coccidioides</i> antibody by enzyme linked immunoassay testing (EIA-IgG) on Day 1, and has positive EIA-IgG at both Days 22 and Day 29
All serologic testing for a single participant from Day 1 through Day 29 will be batched and run concurrently to eliminate confounding due to test run variability.
Absolute values will be recorded for serologic tests, where appropriate, and Indeterminate/Equivocal test results will be treated as a Negative test.

Exploratory Outcome 6:

- The mean, median, and quartiles of the FLEET CAP score at Day 1 in subjects who meet the protocol defined primary case definition and subjects who do not meet the protocol defined primary case definition.

-
- The mean, median, and quartiles for each component of the FLEET CAP score at Day 1 in subjects who meet the protocol defined primary case definitions and subjects who do not meet the protocol defined primary case definition.
 - Cough
 - Fatigue
 - Chest Pain
 - Dyspnea (Shortness of breath)
 - Sputum production
 - Night Sweats
 - Fever
 - Hypoxia

Exploratory Outcome 7:

- The proportion of subjects who received at least one dose of the intervention and who exhibit an increase in liver function tests from baseline (pre-treatment Day 1) as defined as: confirmed AST elevation of >5X ULN or greater than or equal to 225 IU/L or ALT elevation of >5X ULN or greater than or equal to 250 IU/L or total bilirubin elevation >1.5X ULN or aminotransferase elevation of >3X ULN accompanied by total bilirubin elevation >1.5X ULN.

Exploratory Outcome 8:

- The adherence to long term self-administration of daily medications will be assessed in this order of precedence:
 - First: The mean number of pills taken as assessed by pill-count on Days 22, 29 and 43.
 - Second: Subject self-reported adherence as reported on Days 22, 29 and 43.

Exploratory Outcome 9:

- The proportion of subjects with a detectable fluconazole level as assessed by blood test on Days 22 and 43 in fluconazole recipients.
 - Plasma fluconazole concentration will be determined by high-performance liquid chromatography (HPLC)

4. STUDY DESIGN

This trial is a Phase IV randomized, double-blinded, placebo-controlled study in *Coccidioides* endemic regions in 1000 individuals aged 18 years or older, with community acquired pneumonia (CAP) who meet all eligibility criteria. This study is designed to provide data on the efficacy of early antifungal treatment (fluconazole, 400 mg/day) vs. placebo in subjects with coccidioidomycosis pneumonia. Patients who are prescribed antibacterials by their health care provider for acute CAP will be randomized to receive either placebo or 400 mg/day of fluconazole for 42 days.

Blood work for serologic determination of coccidioidomycosis infection will be drawn at the time of randomization (Day 1), and again on Days 22, 29, and 43. On Day 43, subjects will be informed of their treatment assignment and results of serologic testing from Days 1, 22 and 29. At Day 43, those subjects who did not meet the protocol defined case definition for CAP caused by acute coccidioidomycosis and who did not receive fluconazole will be dismissed from the study and referred to a health care provider with the results of their serology testing and their treatment assignment. All subjects who received fluconazole will be evaluated for safety follow-up at Day 49. At Day 49, those subjects who did not meet the protocol defined case definition for CAP caused by acute coccidioidomycosis be dismissed from the study and referred to a health care provider with the results of their serology testing and their treatment assignment. Subjects who did meet the protocol defined case definition for CAP caused by acute coccidioidomycosis infection will be referred to a healthcare provider with the results of their serology testing and their treatment assignment for further treatment as indicated and will be contacted by telephone on Days 90 and 180. Blood samples will be drawn for safety assessments prior to randomization (Day 1) and again on Days 22, 29 and 43. SAEs, as defined in the protocol, will be collected through Day 49.

The primary clinical outcome will be the proportion of subjects meeting the protocol defined case definition who achieve a clinical response to empiric fungal therapy at Day 22 (based on signs and symptoms of pneumonia via FLEET CAP score).

Secondary outcomes will be measured and include the proportion of subjects with coccidioidomycosis pneumonia who achieve clinical response at Day 43; the mean, median and quartiles for both individual components and composite symptom scores over the evaluable points during the duration of the study period; the time missed from work or school; the SF-12v2; and the numbers of all-cause mortality among subjects with coccidioidomycosis pneumonia.

Exploratory outcomes include: the time to determination of positive serology in both treatment groups; the mean, median and quartiles for individual and composite Extra-Pulmonary Symptom Scores in the absence of disseminated disease; time to onset of dissemination; and the change in FLEET CAP score and its individual components over time among patients with

coccidioidomycosis pneumonia receiving placebo. Further exploratory outcomes include; the safety of empiric fluconazole in this population, specifically with respect to liver function testing; and the adherence to long-term drug administration during this study. Parallel analyses of the primary and secondary outcomes will be performed in subjects satisfying an alternative case definition of coccidioidomycosis pneumonia.

As obtaining samples for future use research has an immense potential value for the scientific community, future use samples will be collected in this study. Please see Section 14.8 for further details.

4.1. Sub-studies

Any proposed sub-study that will be added at a future time will be approved by NIAID. All sub-studies will require, in addition, an independent protocol and IRB approval.

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. Subject Inclusion Criteria

Subjects eligible to participate in this study must meet all of the following inclusion criteria:

1. Aged ≥ 18 years and presenting for clinical care in coccidioidomycosis endemic areas.
2. Have a health care provider who has decided to treat community acquired pneumonia with antibacterials.
3. Be able to take and tolerate oral antibacterials/antifungals.
4. Able to understand the study and provide informed consent.
5. Willing and able to comply with study procedures and complete study visits.
6. Willing to allow access to medical records, and medical records are available to the study team.
7. The first dosage of study drug will be administered within 72 hours of presentation for care.
8. Able to swallow large pills.
9. Sexually active female subjects must be of non-childbearing potential* or, if of childbearing potential, must use a highly effective method of birth control**(captured on the appropriate data collection form)

*Non-childbearing potential is defined as being post-menopausal for at least 18 months or surgically sterile via bilateral oophorectomy or hysterectomy.

**Female subjects must avoid becoming pregnant by using one of the following acceptable methods of birth control for 30 days prior to study drug dosing and must be maintained for 30 days after last dose of study drug:

- a. Intrauterine contraceptive device; OR
 - b. Oral contraceptives; OR
 - c. Implanon®, Nexplanon®, DepoProvera®, contraceptive skin patch or NuvaRing®; OR
 - d. Tubal ligation; OR
 - e. Exclusively same-sex relationships
10. Non-pregnant female subjects of childbearing potential must have a negative pregnancy test within 24 hours prior to enrollment and at Visits 02 - 03.
 11. Subjects receiving any of the drugs reported to have manageable drug interactions with fluconazole (see section 6.6.2: Drug Interactions with Fluconazole) are allowed to be enrolled based on PI clinical judgment.

5.2. Subject Exclusion Criteria

Subjects eligible to participate in this study must not meet any of the following exclusion criteria:

1. Have recently received an experimental agent* or participating in or planning to participate in a study involving an experimental agent** while in the active drug administration phase of this study.
* defined as within 30 days prior to enrollment in this study
**(e.g., vaccine, drug, biologic device, blood product, or medication)
2. Present clinical diagnosis of hospital acquired pneumonia (HAP).
3. Documented microbiologically- or serologically-confirmed past infection with coccidioidomycosis.
4. Clinical diagnosis of coccidioidal infection that is of sufficient certainty as to exclude the need for antibacterial therapy.
5. Have a history of systemic antibacterial treatment for this current CAP care episode occurring greater than 4 weeks prior to enrollment.*
*Receipt of systemic antimicrobial therapy for indications other than respiratory tract infection is permitted.
6. Have a history of systemic antifungal treatment within the 4 weeks prior to enrollment.
*A single dose of fluconazole (ex. treatment of vulvovaginal candidiasis) is acceptable and should not exclude subject from study
7. Long term use* of high dose oral or parenteral glucocorticoids**; or high-dose inhaled steroids*** taken within the 4 weeks prior to enrollment.
*defined as > 8 weeks of daily use
**high dose defined as prednisone \geq 20 mg total daily dose, or equivalent dose of other glucocorticoids
***high dose defined as >800 mcg/day of beclomethasone dipropionate or equivalent
8. Have confirmed or suspected immunosuppression as a result of an underlying illness [other than well controlled HIV infection], primary immunodeficiency, or treatment, or induction/maintenance use of immunosuppressive agents*.
*including anti-neoplastic chemotherapy or cytotoxic radiation therapy for cancer, anti-TNF medications, or other immunomodulating agents
9. History of a solid organ or bone marrow transplant.
10. Have poorly controlled HIV-infection or HIV-infection treated with Lopinavir, Tipranavir, Etravirine or Didanosine. Poorly controlled HIV is defined as HIV RNA > 50 copies/mm³ (or greater than the lower limit of quantification [LLOQ] of the local HIV RNA assay if the LLOQ is >50) in the 6 months prior to current care

- episode regardless of whether patient is on antiretroviral therapy or CD4 < 250 cell/mm³.
11. Current diagnosis and/or treatment of active liver disease including abnormal baseline liver function tests as defined as: total bilirubin greater than or equal to 3.0mg/dL AND either AST greater than or equal to 135 IU/L OR ALT greater than or equal to 150 IU/L.
 12. On hemo or peritoneal dialysis or have a creatinine of ≥ 2.0 mg/dL or estimated CrCl ≤ 50 mL/min.
 13. History of hypokalemia defined as less than 3.5 mEq/L on more than one occasion during the 4 weeks prior to enrollment.
 14. History of cardiovascular disease with increased risk for torsades de pointes as defined as:
 - a. NYHA Heart Failure Criteria III or greater; OR
 - b. History of atrial or ventricular dysrhythmias; OR
 - c. History of structural heart disease (including previously repaired); OR
 - d. Personal or family history of congenital long QT syndrome.
 15. A marked baseline prolongation of the QT/QTc interval as defined as a QTc interval > 450 milliseconds (ms) for male subjects or > 470ms for female subjects with repeated demonstration*.

* Subjects without a history of prolonged QTc and an abnormal baseline QTc interval should undergo repeat ECG assessment within screening period prior to randomization (72 hours) to confirm prolongation. If the repeat ECG QTc is within normal limits and less than the parameters above, the subject may be considered for enrollment.
 16. Pregnant or lactating females.
 17. History of azole intolerance or allergy.
 18. Individuals for whom study participation would not be in their best interest, as determined by the clinical investigator.
 19. Are taking medications that are contraindicated with concurrent use of fluconazole (See Section 6.6.1: Contraindicated Medications).
 20. Positive point of care HIV test at Day 1 visit consistent with new HIV diagnosis.

5.3. Treatment Assignment Procedures

5.3.1. Randomization Procedures

Per International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP), screening records will be kept at each participating site to document the reason why an individual was screened, but failed trial entry criteria. The reasons why individuals failed

screening will be recorded in the Statistical and Data Coordinating Center's (SDCC) AdvantageEDCSM (Electronic Data Capture System).

Using a centralized randomization system, eligible subjects will be randomly assigned to 1 of 2 groups (1:1 ratio) to receive either 42 days of placebo or 400 mg/day fluconazole capsules. The randomization code will be prepared by statisticians at the SDCC and sent to the DMID Clinical Agents Repository where the study product will be labeled with a randomization code which links to the treatment assignment. Once consented and determined to be eligible for the trial, the subject will be assigned the next available assignment in sequence of the product available at the site. The randomization code of the distributed study product will be entered into AdvantageEDC upon enrolling the subject in the trial. Instructions for use of the enrollment module are included in the AdvantageEDC User's Guide.

If emergency unblinding is required, the site may determine the treatment assignment by contacting the SDCC or through AdvantageEDC.

Subjects who sign the informed consent form and are randomized but do not ingest the study drug will be replaced. Subjects who sign the informed consent form, and are randomized, receive the study drug, and subsequently withdraw consent, are withdrawn or terminated from the study, or are lost to follow-up will not be replaced.

5.3.2. Masking Procedures

This is a double-blind, randomized clinical trial.

Subjects, investigators, study personnel performing any study-related assessments following study drug administration, and laboratory personnel performing antibody assays will be blinded to group assignment until all study assessments through the Day 43 visit are completed.

The randomization scheme will be generated by the SDCC. In case of a need for emergency unblinding, in order to disclose the assignment to the subject health care providers, the site may determine the treatment assignment through AdvantageEDC or by contacting the SDCC. The site will notify DMID and the appropriate IRB(s) immediately in the event of emergency unblinding. Refer to Section 6.7 for criteria for removing subjects from treatment and initiation of rescue procedures.

On Day 43, subjects will be informed of their treatment assignment and results of serologic testing from Days 1, 22, and 29. For the remainder of the study, subjects will know if they met the primary case definition of CAP caused by acute coccidioidomycosis infection. See the appropriate section of the Manual of Procedures for the appropriate sequence of events prior to informing the subjects if they met the protocol defined case definition of CAP caused by acute coccidioidomycosis infection.

Subjects who withdraw or are terminated from the study will be provided their treatment assignment. When available, the subject will be informed if the subject met the protocol defined

case definition of CAP caused by acute coccidioidomycosis. In addition, subjects will be provided with all available Coccidioidal serologies results.

5.3.3. Reasons for Withdrawal and Discontinuation of Study Product Administration

Subjects may voluntarily withdraw their consent for study participation at any time and for any reason, without penalty. Subjects may also withdraw voluntarily from receiving the study intervention for any reason. An investigator may also withdraw a subject from receiving the study intervention for any reason. If a subject withdraws or is withdrawn prior to completion of the study, the reason for this decision must be recorded in the case report forms (CRFs). Follow-up safety evaluations will be conducted, if the subject agrees.

5.3.3.1. Discontinuation from Treatment

In addition, a subject will be discontinued from the active treatment and continue to be followed if the subject meets any of the following reasons:

- If any of the following criteria for liver-related adverse events are met and confirmed:
 - AST elevation of >5X ULN or greater than or equal to 225 IU/L or
 - ALT elevation of >5X ULN or greater than or equal to 250 IU/L or
 - Total bilirubin elevation >1.5X ULN or
 - Aminotransferase elevation of >3X ULN accompanied by total bilirubin elevation >1.5X ULN
- If any subject experiences any of the following:
 - QTc prolongation as defined by a corrected QT of > 500ms OR > 60ms above baseline measurement
 - Torsades de pointes (torsades, TdP)
 - Unexplained Syncope
 - Seizure in non-epileptic patients
- Medical disease or condition, or any new clinical findings that meet an exclusion criterion or for which continued participation, in the opinion of the site principal investigator or appropriate sub-investigator, would compromise the safety of the subject, would interfere with the subject's successful completion of the study, or would interfere with the evaluation of responses.
- A SAE as defined in the protocol. The subject will be followed until the resolution of the event.

-
- Pregnancy. The subject will be followed up to two months after delivery.
 - New information becomes available that makes further participation unsafe or no longer in the best interest of the subject.
 - Diagnosis of disseminated coccidioidomycosis.
 - Subsequent hospitalization for this CAP episode occurring greater than 72 hours after study randomization.
 - Worsening oxygenation: need for assisted ventilation including continuous positive airway pressure (CPAP), bilevel positive airway pressure (BIPAP), or mechanical ventilation.
 - Unable to adhere to scheduled study visits (e.g. relocation at a distance from the study center that precludes adherence)
 - Determined by a physician's discretion to require additional therapy not indicated in the protocol to ensure his/her health and well-being.

5.3.3.2. Withdrawal from Study Follow-Up

A subject will be withdrawn from the study if the subject meets any of the following reasons. The subject will be informed of their treatment assignment before being withdrawn from the study.

- As deemed necessary by the site principal investigator or appropriate sub-investigator for noncompliance or other reasons.
- Subject withdrawal of consent.
- Subject lost to follow-up.
- Termination of the study.

5.3.4. Handling of Withdrawals and Discontinuation of Administration

The primary reason for withdrawal from the study will be recorded on the Study Status data collection form. Subjects will be encouraged to complete the Early Termination Visit. The Early Termination Visit procedures are listed in Section 7.6. Although subjects are free to withdraw at any time or may be withdrawn by the site principal investigator or appropriate sub-investigator at any time, subjects who receive at least one dose of the study drug will be encouraged to remain in the study for follow-up safety assessments and collection of clinical outcome data. Every attempt will be made to follow all serious adverse events ongoing at the time of early withdrawal to resolution.

In the case of subjects who fail to appear for a follow-up safety assessment, extensive effort (i.e., three documented contact attempts via phone calls, e-mails, etc., made on separate occasions and

followed by a certified letter) will be made to locate or recall them, or at least to determine their health status. These efforts will be documented in the subject's records.

See the appropriate section of the Manual of Procedures (MOP) for alternate follow-up requirements.

5.3.5. Subject Replacement

Subjects who withdraw consent, are withdrawn or terminated from the study, or are lost to follow-up after signing the informed consent form, randomization, and after ingesting study drug will not be replaced. Those subjects who withdraw or are terminated from the study before ingestion of the study drug will be replaced.

5.3.6. Termination of Study

Although the study Sponsor has every intention of completing the study, it reserves the right to terminate the study at any time for clinical or administrative reasons. Reasons for termination include, but are not limited to, study closure due to DSMB review and recommendation; and/or at the discretion of DMID.

6. STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1. Study Product Description

Fluconazole is the first of a new subclass of synthetic triazole antifungal agents. It is designated chemically as 2,4-difluoro-alpha, alpha1,1-bis(1H-1,2,4-triazol-1-ylmethyl) benzyl alcohol with an empirical formula of C₁₃H₁₂F₂N₆O and molecular weight of 306.3.

6.1.1. Acquisition

Fluconazole Capsules

AAIPharma Services Inc. will perform the encapsulation, packaging and labeling of study drug according to applicable regulatory requirements. Fluconazole will be acquired through the DMID Clinical Agents Repository (CAR, Fisher BioServices).

Fluconazole will be shipped from the DMID CAR to the study site upon request and approval by DMID.

Placebo Capsules

AAIPharma Services Inc. will perform the encapsulation, packaging and labeling of study drug according to applicable regulatory requirements. Placebo will be acquired through the DMID Clinical Agents Repository (CAR, Fisher BioServices).

Placebo will be shipped from the DMID CAR to the study site upon request and approval by DMID.

6.1.2. Formulation, Packaging, and Labeling

Fluconazole Capsules

Fluconazole will be supplied as 200mg over encapsulated tablets. Each gelatin capsule will contain two-100mg fluconazole tablets and microcrystalline cellulose for overfill. All study product will be packaged in identical containers each containing 34 capsules. Each container will also be labeled in compliance with applicable regulatory requirements, including the FDA-required cautionary statement “Caution- New drug -Limited by Federal (or United States) Law to Investigational Use Only.”

Placebo Capsules

Placebo will be supplied as matching gelatin capsules containing microcrystalline cellulose only. In order to maintain the blind, the gelatin capsules are the same size, weight, and color as the capsules containing fluconazole tablets. All study product will be packaged in identical containers each containing 34 capsules. Each container will also be labeled in compliance with

applicable regulatory requirements, including the FDA-required cautionary statement “Caution- New drug -Limited by Federal (or United States) Law to Investigational Use Only.”

6.1.3. Product Storage and Stability

Fluconazole

Fluconazole capsules must be stored at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].

Placebo

Placebo capsules must be stored at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].

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

Fluconazole

Fluconazole 400 mg (administered orally as two 200mg capsules) once daily for a minimum of 42 days.

Pills should be maintained as dispensed and not scored, cut, crushed, or otherwise divided for ease of swallowing. The capsules will be administered with water sufficient for the subject to swallow the required number of capsules.

Placebo

Placebo (administered orally as two matching placebo capsules) once daily for a minimum of 42 days.

Pills should be maintained as dispensed and not scored, cut, crushed, or otherwise divided for ease of swallowing. The capsules will be administered with water sufficient for the subject to swallow the required number of capsules.

6.3. Modification of Study Intervention/Investigational Product for a Subject

No modifications of study product are planned at this time. If a subject experiences an allergic reaction to the study drug, they will be taken off of the study drug.

6.4. Accountability Procedures for the Study Intervention/Investigational Product(s)

After receipt of the study product, the site principal investigator (PI) is responsible for distribution and disposition of these study products, and has ultimate responsibility for drug

accountability. The site PI may delegate this responsibility to the site pharmacist. Study product records must be maintained and document logs of receipt, accountability, and storage temperature conditions. These study product accountability and dispensing logs must be maintained in the study file. Upon completion of the study and after the final monitoring visit, unused study product will be retained until monitored and released for disposition as per the Sponsor. For hospitalized subjects, study product will be handled, stored and administered according to procedures outlined in the protocol-specific MOP as appropriate. See above for specific storage conditions for the study product.

6.5. Assessment of Subject Compliance with Study Intervention/Investigational Product/Investigational Device

The investigator will maintain records documenting all study product administered to each subject for the entire study period. For hospitalized subjects, procedures for documentation of study product administration are outlined in the protocol-specific MOP as appropriate. Subjects will be asked to bring their study product containers to each study visit and will be interviewed regarding medication adherence. The study staff will document any missed doses of study medication by counting any pills remaining in the subjects' containers brought to the visit and provide counseling per study sites' routine procedures to promote adherence to study medication. If the subjects' study product containers are lost or unavailable, subject interview will be used to determine study medication adherence. The study staff will record how study drug adherence information was obtained.

6.6. Concomitant Medications/Treatments

Administration of any medications, therapies, or vaccines will be recorded on the appropriate data collection form. Concomitant medications will include all current medications and medications taken within 30 days prior to signing the informed consent form through Day 43 for all subjects. Prescription and over-the-counter drugs will be included as well as vitamins and supplements.

Use of new medication should prompt evaluation for the presence of a new diagnosis of chronic medical disease or condition.

Any other systemic antifungal not provided as part of the study intervention is prohibited during the treatment period of this study, and prohibited within the 4 weeks prior to enrollment (with the exception of a single dose of fluconazole) as specified in Exclusion Criterion 6.

Medications that might interfere with the evaluation of the investigational product should not be used unless absolutely necessary. Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Subjects treated with fluconazole who are concomitantly treated with drugs with a narrow therapeutic window metabolized through CYP2C9 and CYP3A4 should be

considered for additional monitoring of blood levels, lack of efficacy, or increased toxicity of these medications.

The following lists are derived from the FDA package insert and from the information in Up to Date®. It is not a complete list of potential drug-drug interactions, but are lists of agents that are likely to be seen in an ambulatory population.

Antibacterial medications that are prescribed by the health care provider for the treatment of community acquired pneumonia are also not included on this list but are discussed in Section 2.3.1.

Medications in this category include, but are not limited to the following:

6.6.1. Contraindicated medications

Subjects receiving or who have received in the past 30 days prior to enrollment these CONTRAINDICATED medications (Category D and X per Lexi-Comp interaction analysis) will be excluded from the study (Exclusion Criterion 19):

1. Pimozide (Orap®)
2. Quinidine or Quinine
3. Vitamin K Antagonists including Warfarin (Coumadin®)
4. Phenytoin (Dilantin®)
5. Rifampin (Rifadin®) and other Rifamycin derivatives (Rifapentine, Rifabutin)
6. Tofacitinib (Xeljanz® or Jakvius®)
7. Methadone
8. Sirolimus (Rapamune®), Tacrolimus (Prograf®), Everolimus (Afinitor®)
9. Rivaroxaban (Xarelto®)
10. Citalopram (Celexa®) or Escitalopram (Lexapro®)
11. Quetiapine (Seroquel®)
12. Fluoxetine (Prozac®)
13. Lomitapide (Juxtapid®)
14. Ziprasidone (Geodon®)
15. Thioridazine
16. Paliperidone (Invega®) or Iloperidone (Fanapt®)
17. Amiodarone

18. Sotalol
19. Procainamide
20. Dofetilide
21. Ibutilide
22. Dronedarone
23. Ivabrandine (Corlanor®)
24. Disopyramide
25. Erythromycin [only allowed if prescribed within the past 72 hours]
26. Clarithromycin [only allowed if prescribed within the past 72 hours]
27. Ospemifene (Osphena®)
28. Tolvaptan (Samsca®)

6.6.2. Drug Interactions with Fluconazole

The following drugs have been reported to have drug interactions with fluconazole but are not contraindications for concomitant dosing. If a potential subject is receiving one of these medications, use clinical judgment to assess potential safety impact of the agent based on its dose and expected duration of use:

1. Sulfonylureas oral hypoglycemic (Talbutamide®, Glipizide® etc)
2. Theophylline
3. Triazolam (Halcion®)
4. Amitriptyline (Elavil®) or Nortriptyline (Pamelor®)
5. Celecoxib (Celebrex®)
6. Carbamazepine (Tegretol®)
7. Cyclosporin (Sandimmune® - systemically administered)
8. Statins (Lipitor®, Zocor®, Crestor®, etc)
9. Losartan (Cozaar®)
10. Vitamin A
11. Calcium channel blockers (Norvasc®, Procardia®, etc.)
12. Short-acting benzodiazepines (Versed®, Halcion®)

-
13. Vardenafil (Levitra®) or Avanafil (Stendra®)
 14. Zolpidem (Ambien ®)
 15. Ranolazine (Ranexa®)
 16. Tizanidine (Zanaflex®)
 17. Suvorexant (Belsomra®)
 18. Solifenacin (Vesicare®)
 19. Eplerenone (Inspra®)
 20. Clopidogrel (Plavix ®)
 21. Fentanyl (Duragesic®)
 22. Buspirone (Buspar ®)
 23. Cilostazol (Pletal®)
 24. Colchicine

6.7. Rescue Procedures

Subjects who meet any of the following criteria will be removed from the treatment arm, informed of their treatment assignment, and referred to a healthcare provider for continuing of care.

1. Subsequent hospitalization for this CAP episode occurring greater than 72 hours after study randomization.
2. Worsening oxygenation: need for assisted ventilation including continuous positive airway pressure (CPAP), bilevel positive airway pressure (BIPAP), or mechanical ventilation.
3. Determined by a physician's discretion to require additional therapy not indicated in the protocol to ensure his/her health and well-being

After a subject meets one of these criteria, they will be referred back to the health care provider. All available coccidioidal serologic results will be made available to the subject. All participants will be invited to remain in study follow-up. Participants who discontinue treatment due to rescue therapy may be eligible to participate in another study for an alternative coccidioidomycosis pneumonia treatment.

7. STUDY SCHEDULE

7.1. Pre-Screening Assessment [Optional] (occurring up to 72 hours prior to enrollment)

NOTE: For situations in which performance of safety laboratory assessments in advance of screening visit allow for greater feasibility. For patients referred to study with existing standard of care safety labs, physical exam, and/or ECG within the past 72 hours and are available to the study team at the time of screening, these SOC activities can serve as the screening activities and do not require repeating. (Safety laboratory tests are required to have the same normal range values as the primary study site).

The following activities will be performed:

- Provide potential subjects with an abbreviated description of this trial and ask them to read and sign the pre-screening informed consent form. The pre-screening informed consent form will be signed prior to performing any screening procedures.
- Perform an HIV antibody test (point of care (POC) or local clinical laboratory)
- Collect approximately 10 mL of venous blood for Hepatic function panel (AST, ALT, Alkaline phosphatase and total bilirubin), BUN, Creatinine.
- Record a resting (5-minute rest period) 12-lead ECG.
- Notify the potential subject that they will receive a telephone call with the results of the safety laboratory testing (including: AST, ALT, Alkaline phosphatase and total bilirubin, BUN and creatinine) and ECG results to review and explain test results and whether they are eligible to participate in the study. Subjects without a history of prolonged QTc, whose baseline ECG shows prolonged QTc interval may be asked to return for repeat 12-lead ECG prior to determination of eligibility status. Eligible subjects will be asked to return for enrollment visit with the study team.
- The investigator will inform the subject of the results of the POC HIV -1 antibody test and provide counseling as to the meaning of the results, whether positive or negative. If the POC HIV-1 antibody test is positive and the participant does not have a prior diagnosis of HIV infection, the subject will be no longer be considered eligible for participation in the study. Counseling regarding the preliminary result and the need for a confirmatory test should be done by the site research team. A positive confirmatory test for those patients with a positive POC HIV testing will require counseling about the results and a recommendation to follow-up for care, preferably in person. Newly diagnosed HIV infections will receive additional counseling concerning the significance and possible risks to other people. Individuals with newly diagnosed HIV infections will be referred to the subjects' clinical care provider and

any other appropriate local resource. All test results, positive or negative, will be kept confidential to the extent permissible under the law. All positive results will be reported to the state's Division of Public Health as required by law. All confirmatory testing will be done following the institution's policy or the standard of care.

7.2. Screening/Enrollment/Baseline (Day 1, Visit 01)

NOTE: If referred to the study from another facility, potential subjects should be screened only if the subject can be enrolled and first dosing of study product will occur within 72 hours from discharge from the facility in where the decision to treat with antibacterials for CAP has occurred. For patients referred to study with existing standard of care safety labs, physical exam, and/or ECG within the past 72 hours and are available to the study team at the time of screening, these SOC activities can serve as the screening activities and do not require repeating. (Safety laboratory tests are required to have the same normal range values as the primary study site). The following activities will be performed:

- Provide subjects with a description of this trial and ask them to read and sign the informed consent form. The informed consent form will be signed prior to performing any study procedures, including any screening procedures.
- Collect demographic data including employment status and school/education enrollment.
- Review eligibility criteria with subjects.
- Review medical records to ensure eligibility.
- Record date of X-ray, if a chest X-ray was performed in establishing the diagnosis of this episode of CAP.
- Interview subjects and obtain medical history.
- Record medication history including the name and total daily dose of medication over the past 30 days, including vitamins, over-the-counter, and prescription drugs.
- Record vital sign measurements (sitting blood pressure, sitting heart rate, respiratory rate, oral temperature and oxygen saturation), height and weight.
- Record a resting (5-minute rest period) 12-lead ECG. (will not need to be repeated if completed as part of pre-screening assessment)
- Complete physical examination by a clinician licensed to make medical diagnoses.
- Complete FLEET CAP Score
- Complete Extra-Pulmonary Symptom Score

-
- Complete SF-12v2
 - Complete PROMIS Item Bank v2.0 - Ability to Participate in Social Roles and Activities - Short Form 4a
 - Perform a urine or serum pregnancy test on all women of childbearing potential. Test must be negative to ensure eligibility.
 - Perform a point of care (POC) HIV antibody test. (will not need to be repeated if completed as part of pre-screening assessment)
 - Collect approximately 10 mL of venous blood for Hepatic function panel (AST, ALT, Alkaline phosphatase and total bilirubin), BUN, Creatinine. (will not need to be repeated if completed as part of pre-screening assessment)
 - Collect approximately 15 mL of venous blood for Coccidioidal serologies (CF; qualitative IDCF and IDTP; EIA-IgM; EIA IgG; and quantitative IDCF)
 - In addition the subject will be allowed the option to consent for additional sample collection (urine specimen, blood specimen [20 mL], nasopharyngeal swab, and throat swab) to be banked and used in future studies
 - The investigator will inform the subject of the results of the POC HIV -1 antibody test and provide counseling as to the meaning of the results, whether positive or negative. If the POC HIV-1 antibody test is positive and the participant does not have a prior diagnosis of HIV infection, the subject will no longer be considered eligible for participation in the study and the study product should not be administered. Counseling regarding the preliminary result and the need for a confirmatory test should be done by the site research team. A positive confirmatory test for those patients with a positive POC HIV testing will require counseling about the results and a recommendation to follow-up for care. Newly diagnosed HIV infections will receive additional counseling concerning the significance and possible risks to other people. Individuals with newly diagnosed HIV infections will be referred to the subjects clinical care provider and any other appropriate local resource. All test results, positive or negative, will be kept confidential to the extent permissible under the law. All positive results will be reported to the state's Division of Public Health as required by law. All confirmatory testing will be done following the institution's policy or the standard of care.
 - The investigator must review all safety laboratory results (including: AST, ALT, Alkaline phosphatase and total bilirubin, BUN, and creatinine), ECG results for QT prolongation, pregnancy test results, POC HIV test and eligibility criteria before the subject is randomized. Subjects who do not qualify for the study based on the results of the screening procedures

should not be randomized. Subjects whose baseline ECG shows prolonged QTc interval may be asked to return for repeat 12-lead ECG prior to determination of eligibility status. Counseling regarding POC HIV testing and risk of false positives should occur by the site research team prior to the test being done.

- Enroll subjects in AdvantageEDC.
- Dispense the next available treatment assignment in sequence of study product (fluconazole or placebo) available at the site. Regardless of time the product is dispensed, observe subject taking 2 capsules (at once) in the clinic, and instruct subject to select a time of day to take their daily dose. If dosing cannot occur within 72 hours of the discharge from the facility where antibacterials for CAP were prescribed, then the subject should not be dosed and study activity must cease. Ideally, pills should be taken at the same time each day. Instruct subjects to bring their pill bottles to each visit. Review with subject that the study product should be stored at room temperature. Dispense 2 study product bottles (bottle A and B).
- Instruct subjects to notify the study center if they develop any severe reactions after study product dosing. If the site principal investigator or appropriate sub-investigator deems the reaction severe enough, further instructions will be given to the subject on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.

Documentation of the subject's fulfillment of the entry criteria, for all subjects considered for the study and subsequently included or excluded, is to be completed. Documentation of screening failure details may be recorded using eligibility screening forms or a subject screen failure log. Screen failures will be entered in AdvantageEDC.

7.3. Follow-up (Days 22-180, Visits 02-07)

7.3.1. Follow-up Visit Visit 02 (Day 22):

(Window: Day 20 to Day 23):

- Interview subjects and review the medical record for interim medical history, including an assessment for new medical conditions and symptoms, hospitalizations, diagnosis of disseminated coccidioidomycosis. Note any changes since the previous clinic visit.
- Perform a urine or serum pregnancy test on all women of childbearing potential. The test must be negative to ensure continued eligibility.
- Review any concomitant medications since previous study visit. Record all concomitant medications on the appropriate data collection form.
- Review of inclusion/exclusion criteria by clinician licensed to make medical diagnoses to determine continued eligibility.

-
- Perform a targeted physical examination if indicated based on review of complete medical history and any updates obtained by interview of subjects since the Day 1 visit by a clinician licensed to make medical diagnoses.
 - Record vital sign measurements (sitting blood pressure, sitting heart rate, respiratory rate, oral temperature, oxygen saturation and weight).
 - Query subject regarding whether the subject has taken their dose for today. If the subject has not yet taken their dose for today, subject should be instructed to take the day's dose in the clinic, prior to the pill count.
 - Perform a pill count of study product (fluconazole or placebo) and interview to determine adherence. Review need to bring pill bottles for count to each visit, study product dosing and storage requirements and ability to meet requirements with subject.
 - Following pill count, collect the pill bottle A and retain until study product accountability has been completed by the study monitor.
 - Note any discrepancies between expected and actual pill count remaining in pill bottle B.
 - Review randomization number assigned at Visit 01 and dispense final bottle (bottle C) of study product. Instruct the subject to continue to take daily doses from pill bottle B and to begin taking their daily doses from the newly dispensed bottle (bottle C) once bottle B is empty.
 - If subject did not return the pill bottle A dispensed at Visit 01, instruct them to return this bottle at their next visit.
 - Complete FLEET CAP Score
 - Collect the number of days missed from school and/or work due to illness for subjects who were either enrolled in school or employed at baseline
 - Complete PROMIS Item Bank v2.0 - Ability to Participate in Social Roles and Activities - Short Form 4a
 - Complete Extra-Pulmonary Symptom Score
 - Complete SF-12v2
 - Draw venous blood samples for the following:
 - Safety laboratories (Hepatic function panel (AST, ALT, Alkaline phosphatase and total bilirubin), BUN, Creatinine) [10 mL]

-
- Coccidioidal serologies (CF; qualitative IDCF and IDTP; EIA-IgM; EIA IgG; and quantitative IDCF) [15 mL]
 - Quantitative fluconazole level [5 mL]
 - Blood to be banked for future use if consent obtained [15 mL]
 - Assess any SAEs and record on the SAE form and in AdvantageEDC.

7.3.2. Follow-up Visit 03 (Day 29)

(Window: Day 27 to Day 30)

- Interview subjects and review the medical record for interim medical history, including an assessment for new medical conditions and symptoms, hospitalizations, diagnosis of disseminated coccidioidomycosis. Note any changes since the previous clinic visit.
- Perform a targeted physical examination if indicated based on review of complete medical history and any updates obtained by interview of subjects since the Day 1 visit by a clinician licensed to make medical diagnoses.
- Perform a urine or serum pregnancy test on all women of childbearing potential. The test must be negative to ensure continued eligibility.
- Review any concomitant medications since previous study visit. Record all concomitant medications on the appropriate data collection form.
- Review of inclusion/exclusion criteria by clinician licensed to make medical diagnoses to determine continued eligibility.
- Record vital sign measurements (sitting blood pressure, sitting heart rate, respiratory rate, oral temperature, oxygen saturation and weight).
- Query subject regarding whether the subject has taken their dose for today. If the subject has not yet taken their dose for today, subject should be instructed to take the day's dose in the clinic, prior to the pill count.
- Perform a pill count of study product (fluconazole or placebo) and interview to determine adherence.
- Following pill count, collect the pill bottle (bottle B) and retain until study product accountability has been completed by the study monitor.
- Review need to bring pill bottles for count to each visit, study product dosing, storage at room temperature, and ability to meet requirements with subject.
- Complete FLEET CAP Score

-
- Collect the number of days missed from school and/or work due to illness for subjects who were either enrolled in school or employed at baseline.
 - Complete PROMIS Item Bank v2.0 - Ability to Participate in Social Roles and Activities - Short Form 4a
 - Complete Extra-Pulmonary Symptom Score
 - Complete SF-12v2
 - Draw venous blood samples for the following:
 - Safety laboratories (Hepatic function panel (AST, ALT, Alkaline phosphatase and total bilirubin), BUN, Creatinine) [10 mL]
 - Coccidioidal serologies (CF; qualitative IDCF and IDTP; EIA-IgM; EIA IgG; and quantitative IDCF) [15 mL]
 - Blood to be banked for future use if consent obtained [15 mL]
 - Assess any SAEs and record on the SAE form and in AdvantageEDC.

7.3.3. Follow-up Visit 04 (Day 43)

(Window: Day 42 to Day 46)

NOTE: All assessments for this visit must be completed before the subject or study staff performing the assessments are informed of the treatment assignment and whether they met the protocol definition of acute coccidioidomycosis pneumonia

- Interview subjects and review the medical record for interim medical history, including an assessment for new medical conditions and symptoms, hospitalizations, diagnosis of disseminated coccidioidomycosis. Note any changes since the previous clinic visit.
- Perform a targeted physical examination if indicated based on review of complete medical history and any updates obtained by interview of subjects since the Day 1 visit by a clinician licensed to make medical diagnoses.
- Record vital sign measurements (sitting blood pressure, sitting heart rate, respiratory rate, oral temperature, oxygen saturation and weight).
- Perform a urine or serum pregnancy test on all women of childbearing potential.
- Review any concomitant medications since previous study visit. Record all concomitant medications on the appropriate data collection form.
- Perform a pill count of study product (fluconazole or placebo) and interview to determine adherence.

-
- Following pill count, collect the pill bottle (bottle C) and retain until study product accountability has been completed by the study monitor.
 - Complete FLEET CAP Score
 - Collect the number of days missed from school and/or work due to illness for subjects who were either enrolled in school or employed at baseline
 - Complete PROMIS Item Bank v2.0 - Ability to Participate in Social Roles and Activities - Short Form 4a
 - Complete Extra-Pulmonary Symptom Score
 - Complete SF-12v2
 - Draw venous blood samples for the following:
 - Safety laboratories (Hepatic function panel (AST, ALT, Alkaline phosphatase and total bilirubin), BUN, Creatinine) [10 mL]
 - Coccidioidal serologies (CF; qualitative IDCF and IDTP; and quantitative IDCF) [15 mL]
 - Quantitative fluconazole level [5 mL]
 - Blood to be banked for future use if consent obtained [15 mL]
 - Assess any SAEs and record on the SAE form and in AdvantageEDC.

Subjects will be informed of their treatment group assignment after all assessments for this visit are completed. Subjects will also be informed of the results of serologic testing from Day 01, Day 22 and Day 29 visits. If the subject meets the protocol defined case definition of CAP caused by acute coccidioidomycosis infection, refer the subject to their identified health care provider.

NOTE: All assessments for this visit must be completed before the subject or study staff performing the assessments are informed of the treatment status. For the remainder of the study, follow-up and additional procedures will be determined based on treatment assignment and whether the subject met the protocol definition of acute coccidioidomycosis pneumonia

Coccidioidomycosis Negative Subjects Who Received Placebo

- Subjects will be provided with all available coccidioidal serology results and their treatment group assignment.
- Subjects will be informed that they they did not meet the protocol defined case definition of CAP caused by acute coccidioidomycosis infection.

-
- Refer subject to their health care provider with information as to treatment group assignment and disease status.
 - Those subjects who did not meet the protocol defined case definition of CAP caused by acute coccidioidomycosis infection will be dismissed from the study following data collection and referral.

Coccidioidomycosis Positive Subjects Who Received Placebo

- Subjects will be provided with all available coccidioidal serology results and their treatment group assignment.
- Subjects will be informed that they met the protocol defined case definition of CAP caused by acute coccidioidomycosis infection.
- Refer subject to their identified health care provider with for evaluation of need for initiation of treatment and clinical follow-up.

All coccidioidomycosis positive subjects will be followed through Day 180. These subjects will be provided the visual analogue scale and instructed on its measurement for assessment of extra-pulmonary symptom score for use during follow up phone visits (Visits 06 and 07) as well as with addressed/stamped envelope for returning to study team.

Coccidioidomycosis Positive and Negative Subjects Who Received Fluconazole

- Remind subject that contraceptives must be maintained until 30 days after the last dose of study medication.
- Refer to Section 5.2

7.3.4. Follow-up Visit 05 (Day 49) – Telephone follow-up for those subjects randomized to Fluconazole only:

(Window: Day 48 to Day 51)

Follow-up and additional procedures will vary according to randomization group and Coccidioidomycosis status.

Coccidioidomycosis Negative Subjects Who Received Fluconazole

- Subjects will be reminded that they they did not meet the protocol defined case definition of CAP caused by acute coccidioidomycosis infection.
- Subjects who were randomized to fluconazole will be queried for SAE collection and referred to their health care provider with results of the safety lab testing for follow-up if abnormalities are noted.
- Remind subject that contraceptives must be maintained until 30 days after the last dose of study medication.

-
- Those subjects who did not meet the protocol defined case definition of CAP caused by acute coccidioidomycosis infection will be dismissed from the study following data collection and referral.

Coccidioidomycosis Positive Subjects Who Received Fluconazole

- Subjects will be reminded that they met the protocol defined case definition of CAP caused by acute coccidioidomycosis infection.
- Subjects who were randomized to fluconazole will be queried for SAE collection and referred to their health care provider with results of the safety lab testing for follow-up if abnormalities are noted.
- Remind subject that contraceptives must be maintained until 30 days after the last dose of study medication.
- Refer subject to their identified health care provider with for evaluation of need for continued treatment and clinical follow-up.

7.3.5. Follow-up Visit 06 (Day 90): Telephone Follow-up for Coccidioidomycosis Positive Subjects Only

(Window: Day 83 to Day 97)

- Complete PROMIS Item Bank v2.0 - Ability to Participate in Social Roles and Activities - Short Form 4a
- Complete SF-12v2
- Instruct subject to complete Extra-Pulmonary Symptom Score and remind subject to mail results to study team.
- Interview the subject and review the subject's medical record for diagnosis of disseminated coccidioidomycosis
- Refer subject to their identified health care provider for clinical follow-up of any ongoing health concerns identified during interview or completion of patient reported outcome measures.

7.3.6. Follow-up Visit 07 (Day 180): Telephone Follow-up for Coccidioidomycosis Positive Subjects Only

(Window: Day 173 to Day 187)

- Complete PROMIS Item Bank v2.0 - Ability to Participate in Social Roles and Activities - Short Form 4a
- Complete SF-12v2

-
- Instruct subject to complete Extra-Pulmonary Symptom Score and remind subject to mail results to study team.
 - Interview the subject and review the subject's medical record for diagnosis of disseminated coccidioidomycosis
 - Refer subject to their identified health care provider for clinical follow-up of any ongoing health concerns identified during interview or completion of patient reported outcome measures

7.4. Early Termination Visit (if needed)

7.4.1. Before Follow-up Visit 04

The following assessments will be performed at the early termination visit for subjects who withdraw, or are withdrawn or terminated from this study:

- Obtain interim medical/surgical history, including an assessment for new medical conditions and symptoms by interview of subjects and review of the medical record and note any changes since the previous visit.
- Record all concomitant medications on the appropriate data collection form.
- Assess any SAEs and record on SAE form and in AdvantageEDC.
- Complete a targeted physical examination based on symptoms.
- Record vital sign measurements (sitting blood pressure, sitting heart rate, respiratory rate, oral temperature, oxygen saturation and weight).
- Perform urine pregnancy test for women of child-bearing potential.
- Perform a 12-lead ECG if termination occurs before Day 15
- Perform a pill count of study product (fluconazole or placebo) and interview to determine adherence. Following pill count, collect the pill bottle and retain until study product accountability has been completed by the study monitor.
- Complete symptom Assessment including FLEET CAP Score, PROMIS Item Bank v2.0 - Ability to Participate in Social Roles and Activities - Short Form 4a, Extra-Pulmonary Symptom Score and SF-12v2
- Collect the number of days missed from school and/or work due to illness for subjects who were either enrolled in school or employed at baseline.
- Draw venous blood samples for the following:

-
- Safety laboratories (Hepatic function panel (AST, ALT, Alkaline phosphatase and total bilirubin), BUN, Creatinine) [10 mL]
 - Coccidioidal serologies (CF; qualitative IDCF and IDTP; EIA-IgM; EIA IgG; and quantitative IDCF) [15 mL]
 - Quantitative fluconazole level [5 mL]
 - Blood to be banked for future use [15 mL]
 - Contact subject with results of the safety lab testing for follow-up with health care provider if abnormalities are noted.
 - All available coccidioidal serologic results will be made available to the subject. The treatment status will be revealed to the participant. All participants will be invited to remain in study follow-up. Refer subject to their identified health care provider.

7.4.2. After Follow-up Visit 04 A telephone visit will be conducted.

The following assessments will be performed at the early termination visit for subjects who withdraw, or are withdrawn or terminated from this study:

- Assess any SAEs and record on SAE form and in AdvantageEDC if early termination visit occurs after visit 04 but prior to Day 49 in subjects who received fluconazole..
- Complete symptom Assessment including PROMIS Item Bank v2.0 - Ability to Participate in Social Roles and Activities - Short Form 4a and SF-12v2
- Subject will be asked to complete Extra-Pulmonary Symptom Score and mail results to study team
- Review the subject's medical record for diagnosis of disseminated coccidioidomycosis
- Contact subject with results of the safety lab testing for follow-up with health care provider if abnormalities are noted.

7.5. Unscheduled Visit

Unscheduled visits are allowed for the following reasons:

- Management of an SAE.
- Performance of additional laboratory tests or procedures for clinically abnormal test values (e.g., confirming elevated levels of liver enzymes).
- Any time the investigator feels that it is clinically appropriate for subject safety.

The following assessments should be made during unscheduled visits:

- Assess the situation which prompted the unscheduled visit
- Perform a targeted physical exam
- Record vital sign measurements (sitting blood pressure, sitting heart rate, respiratory rate, oral temperature, oxygen saturation and weight).

Unscheduled visits will be labeled and documented by the number of the visit the subject just completed, followed by the letter “S” to denote the first unscheduled visit (e.g. 01S, 02S), the letter “T” to denote second unscheduled visit, etc.

8. STUDY PROCEDURES/EVALUATIONS

8.1. Clinical Evaluations

Complete medical history will be obtained by review of the medical record and interview of subjects on Day 1. Subjects will be queried regarding a history of significant medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic system, nervous system, blood, lymph glands, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, substance abuse, cardiovascular and autoimmune disease will be solicited. On Days 22, 29, and 43, an interim medical history will be obtained by interview of the subjects noting any changes since the previous clinic visit or contact. The interim medical history should include an assessment and review of medical records for new medical conditions and symptoms including any hospitalizations and diagnoses made for disseminated coccidioidomycosis.

Medications history (concomitant medications) will include a review of all current medications and medications taken within 30 days prior to signing the informed consent form through Day 43 or early termination, whichever occurs first. Prescription and over-the-counter drugs will be included as well as herbals, vitamins and supplements. Use of new medication should prompt evaluation for the presence of a new diagnosis of chronic medical disease or condition.

Assessment of eligibility will include a review of all permitted and prohibited medications per the study inclusion and exclusion criteria. In addition, the site principal investigator or appropriate sub-investigator may identify other medications that should not be used due to a risk to subject safety. The site principal investigator or appropriate sub-investigator will decide whether the medications the subjects receive can interact with fluconazole and necessitate further monitoring or dosage adjustment.

At the screening visit a physical examination will be performed by a clinician licensed to make medical diagnoses. A standard of care physical exam completed by a clinical provider within the 72 hours prior to screening may be used for the screening exam if all appropriate organ systems are examined and documented. The comprehensive physical examination must include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; neurological; chest and lungs; cardiovascular; abdomen (liver and spleen); lymph nodes; musculoskeletal, genitourinary and extremities. Assessments of any specific signs or symptoms reported by the subject must also be performed and documented. Findings from the screening must be characterized as either normal or abnormal, and if abnormal, a description of the abnormality must be provided. Following the screening visit physical examination, targeted physical exams will be performed on Days 22, 29, and 43 if indicated based the subject's interim

medical history, and changes must be classified as new, worsened, or improved from those at screening.

Vital signs (sitting heart rate, sitting blood pressure (mmHg), respiratory rate, oral temperature (°C), oxygen saturation (SpO₂)) and weight will be collected at the screening visit, Days 22, 29, and 43. Vital signs assessed on Day 1 will be considered as baseline. Subjects must not eat anything hot or cold or smoke within 10 minutes prior to taking oral temperature. Height will be collected on Day 1.

A resting 12-lead ECG will be performed at Day 1 or the pre-screening visit and at early termination visits when applicable. An ECG completed as part of standard of care within the past 72 hours and that is available to the study team at the time of screening can serve as the screening ECG and does not require repeating. The ECG will be assessed for QT prolongation as well as other abnormalities indicative of QT prolongation while the subject is on-site for their study-related visit by a clinician licensed to make medical diagnoses.

The FLEET CAP score is an efficacy outcome measure based on a clinical scoring system that allows a constellation of clinical symptoms to be quantified and scored over time: cough, fatigue, chest pain, dyspnea, sputum production, night sweats, fever, and hypoxia. The FLEET CAP score will be completed on Days 1, 22, 29, and 43.

The Extra-Pulmonary Symptom Score will be used to rate arthralgia, rash, and headache and will be completed by the subject on Days 1, 22, 29, and 43. After appropriate education on self-measurement using the visual analog scale, coccidioidomycosis positive subjects will be asked to complete this on Day 90 and 180 and return by mail to the study team.

The SF-12v2 uses 12 questions to measure functional health and well-being from the study subject's perspective across eight domains: physical functioning, role, bodily pain, general health perceptions, vitality, social functioning, emotional role, and mental health. The SF-12v2 will be completed by the subject on study Days 1, 22, 29, and 43. For subjects who are coccidioidomycosis positive, the survey will also be collected on Days 90 and 180.

The PROMIS Ability to Participate in Social Roles and Activities - Short Form 4a uses 4 questions to measure the subject's ability to participate in social roles and activities in the context of family, friends, leisure, and work. The PROMIS short form will be completed by the study subjects on study Days 1, 22, 29 and 43. For subjects who are coccidioidomycosis positive, the survey will also be collected on Days 90 and 180.

On study Days 22, 29, and 43, subjects will be queried about time missed from school or work due to illness.

See Section 6.7 for information regarding rescue procedures.

8.2. Laboratory Evaluations

8.2.1. Clinical Laboratory Evaluations

Clinical screening laboratory parameters to be evaluated on Day 1 (or at pre-screening visit) to confirm study eligibility prior to receipt of the first study drug and will include a hepatic function panel (AST, ALT, Alkaline phosphatase, and total bilirubin), BUN, creatinine and HIV-1 POC testing. A urine or serum pregnancy test will be performed in women of child-bearing potential. To be eligible for participation in this trial the subject's clinical screening laboratory evaluations must be confirmed to meet the eligibility criteria as outlined in the Subject Eligibility Criteria.

- The hepatic panel (AST, ALT, Alkaline phosphatase, and total bilirubin), BUN, creatinine and POC HIV-1 testing will be performed by the local or site laboratory with same day resulting. A venous blood sample (approximately 10 mL) will be collected from each subject at the Day 1 or pre-screening visit. Safety labs completed as part of standard of care within the past 72 hours and that are available to the study team at the time of screening can serve as the screening activities and do not require repeating. (Laboratory screening tests are required to have the same normal range values as the primary study site).
- The urine or serum pregnancy test will be performed in women of child-bearing potential will be performed by the local or site laboratory with same day resulting. No additional sample will be needed if a serum test is desired.

Clinical safety laboratory parameters to be evaluated on Days 22, 29 and 43 include hepatic function panel (AST, ALT, Alkaline phosphatase, and total bilirubin), BUN, creatinine and pregnancy test (urine or serum) for women of child-bearing potential. These evaluations will be performed by the local or site laboratory with same day resulting. Venous blood samples (approximately 10 mL) will be collected from each subject on specified study days.

8.2.2. Special Assays or Procedures

8.2.2.1. Coccidioides antibodies for determination of primary and alternative case definitions

Assays to determine Coccidioides antibodies will be performed at Associated Regional and University Pathologist Inc. (ARUP) laboratories. Venous blood samples (approximately 15 mL) will be collected for complement fixation, qualitative immunodiffusion with CF antigen (IDCF) and tube precipitin antigen (IDTP), and enzyme-linked immunoassays for both IgM and IgG on Days 1, 22, and 29.

All serological testing for a single participant from Day 1 through Day 29 will be batched and run concurrently to eliminate confounding due to test run variability.

8.2.2.2. Confirmatory and alternative determination of *Coccidioides* antibodies

Confirmatory testing will be done at the University of California Davis (UC-Davis) utilizing an aliquot from the venous blood samples above collected on Days 1, 22, 29 and 43 using complement fixation, qualitative and quantitative immunodiffusion with CF antigen (IDCF), and qualitative immunodiffusion with tube precipitin antigen (IDTP).

All serological testing from Day 1 through Day 43 for a single participant will be batched and run concurrently to eliminate confounding due to test run variability.

8.2.2.3. Fluconazole Serum Levels

Quantitative fluconazole testing will be performed at ARUP laboratories. Venous blood samples (approximately 5mL at each visit, for a total of 10 mL) will be collected on study Days 22 and 43.

8.2.2.4. Future Use Samples

For those subjects who consent to additional sample collection, blood, urine, throat, and nasopharyngeal samples will be collected for future use studies. Additional venous blood samples (approximately 20mL for Day 1 and 15 mL for subsequent visits indicated) will be collected on study Days 1, 22, 29, and 43. One urine sample, one nasopharyngeal swab, and one throat swab will also be collected on Day 1.

8.2.2.5. Total Blood Volume

Total blood volume collected per participant is approximately 135 mL (200 mL for subjects consenting to additional sample collection for future use).

8.2.3. Specimen Preparation, Handling, and Shipping

8.2.3.1. Instructions for Specimen Preparation, Handling, and Storage

Instructions for specimen preparation, handling and storage are included in the site/local laboratory manual and protocol-specific MOP as appropriate.

8.2.3.2. Specimen Shipment

Specimen shipment will occur at intervals during the course of this study following all applicable International Air Transport Association (IATA) requirements and according to the specifics for storage temperature and documentation as detailed in the central (clinical) laboratory manual and protocol-specific MOP as appropriate.

Specimens for safety laboratory evaluations will be transported from the participating site to the local site laboratory.

Specimens for *Coccidioides* antibodies and fluconazole serum levels will be shipped from the participating sites to the DMID Clinical Repository and provided to ARUP laboratories and UC Davis in a blinded manner.

The frequency and conditions of specimen shipment will be described in the appropriate section of the MOP.

9. ASSESSMENT OF SAFETY

9.1. Specification of Safety Parameters

Fluconazole is an approved drug with an established and well-described safety profile. The most prevalent of the drug side effects include headache (13%), nausea (7%), and abdominal pain (6%). In less than 1% of individuals taking this medication there is a perversion of taste. There are rare reports of exfoliative dermatitis, some of which were fatal. There are reports of liver toxicity (in particular with patients with co-morbidities and previous liver injury), which are not dose dependent.

As fluconazole is an approved drug with a long prescribing history, NIAID does not expect that any new drug related safety signal will be detected in this trial. As such, the safety data collection will be targeted to only collect Suspected Unexpected Serious Adverse Reactions (SUSARs) and congenital anomalies/birth defects.

For individual patients, liver function testing will be performed to monitor for possible liver injury.

9.2. Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1. Adverse Events

Adverse Event (AE): International Conference on Harmonisation (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. FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product.

As the safety profile of fluconazole is well established, and this trial is not powered to detect new, unknown safety signals, **there will be no non-serious AE collection in this trial.**

Relationship to Study Products: The licensed study physician's assessment of a SAE's relationship to study product is part of the documentation process, but it is not a factor in determining what is or is not reported in this trial. If there is any doubt as to whether a clinical observation is an SAE, the event should be reported. The relationship to study product must be assessed for SAEs 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.

9.2.2. Serious Adverse Events

Serious Adverse Event (SAE): 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 site principal investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

Death and life-threatening events are part of the efficacy endpoints of this trial and will not be reported or collected as SAEs unless they meet the criteria below.

Only the following events will be considered SAEs:

- Congenital anomalies or birth defect, OR
- Any condition that meets the regulatory definition of a SAE AND is unexpected (per PI) AND is suspected to be directly caused by the study drug (e.g., anaphylaxis, Stevens-Johnson syndrome, exfoliative dermatitis)

Protocol defined SAEs will be:

- Collected from the time of enrollment through visit Day 49
- Assessed for relationship to study product
- Recorded on the appropriate SAE form and eCRF
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator
- Reviewed and evaluated by DMID, the DSMB (periodic review), and the IRB

9.2.3. Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

Study drug will be stopped for the individual subject if:

- If any of the following criteria for liver-related adverse events are met and confirmed:
 - AST elevation of >5X ULN or greater than or equal to 225 IU/L or
 - ALT elevation of >5X ULN or greater than or equal to 250 IU/L or
 - Total bilirubin elevation >1.5X ULN or
 - Aminotransferase elevation of >3X ULN accompanied by total bilirubin elevation >1.5X ULN
- If any subject experiences any of the following:
 - QTc prolongation as defined by a corrected QT of > 500ms OR > 60ms above baseline measurement
 - Torsades de pointes (torsades, TdP)
 - Unexplained Syncope
 - Seizure in non-epileptic patients

The subject will be referred to an appropriate health care provider for treatment, and will be followed-up until stabilization or resolution.

The abnormal hepatic function testing will be documented on an appropriate eCRF.

Aggregate information regarding abnormalities of hepatic function testing will be presented to the DSMB in their regular meetings.

9.3. Reporting Procedures

9.3.1. Serious Adverse Events

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group, at the following address:

**DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20817, USA
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)
SAE FAX Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)
SAE Email Address: PVG@dmidcroms.com**

In addition to the SAE form, selected SAE data fields must also be entered into AdvantageEDC. Please see the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible.

The DMID Medical Monitor and DMID Clinical Project Manager will be notified of the SAE by the DMID Pharmacovigilance Group. The DMID Medical Monitor 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 site principal investigator or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the site principal investigator or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

9.3.2. Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the site principal investigator or appropriate sub-investigator, DMID, the Investigational New Drug (IND) sponsor, will report any suspected adverse reaction that is both serious and unexpected. DMID 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. DMID will notify FDA and all participating site principal investigators (i.e., all principal investigators to whom the sponsor is providing drug under its IND(s) or under any principal investigator's IND(s)) 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. DMID 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, DMID 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.

9.3.3. Reporting of Pregnancy

Although not AEs, pregnancies are reportable events. Any pregnancies that occur during the study period in women who have received any study product (fluconazole or placebo) will be reported via the AdvantageEDC on the Pregnancy Report form within 5 days of site awareness. The report will include pregnancy outcome (e.g., any premature terminations, elective or therapeutic, any spontaneous abortions or stillbirths), as well as the health status of the mother and child, including date of delivery and infant’s sex and weight. Pregnancies will be followed up to two months after birth. All pregnancies will be reported to the clinical data management group. If the database is locked at time of pregnancy, a supplemental report will be generated and completed after birth and follow-up, which will be appended to the database.

9.4. Type and Duration of Follow-up of Subjects after Adverse Events

SAEs will be followed from the time of enrollment until completion of study even if this extends beyond the study-reporting period. For those subjects who are dismissed from study follow-up after study Day 43 (Visit 04), SAEs will be followed but new SAEs will not be collected. All subjects who received fluconazole will be followed through Day 49. Resolution of an SAE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Follow-up procedures, evaluations, and outcomes will be recorded on the appropriate data collection form.

9.5. Halting Rules

For all subjects:

- A. If more than 10% (and at least 5) of randomized subjects develop clinically significant elevations in liver enzymes as defined below, study enrollment will be halted for DSMB review.
 - If any of the following criteria for liver-related adverse events are met and confirmed:
 - AST elevation of >5X ULN or greater than or equal to 225 IU/L or
 - ALT elevation of >5X ULN or greater than or equal to 250 IU/L or

-
- Total bilirubin elevation >1.5X ULN or
 - Aminotransferase elevation of >3X ULN accompanied by total bilirubin elevation >1.5X ULN
- B. If more than 1% (and at least 2) of the randomized subjects develop QT prolongation or clinical symptoms indicative of symptomatic QT prolongation as defined below, study enrollment will be halted for DSMB review.
- QTc prolongation > 500ms or >60ms above baseline measurement
 - Torsades de pointes (torsades, TdP)
 - Cardiac Sudden death
 - Unexplained Syncope
 - Seizure in non-epileptic patients

The DSMB will review the study for efficacy according to the interim analysis plan.

9.6. Safety Oversight (ISM plus SMC or DSMB)

9.6.1. Independent Safety Monitor (ISM)

The ISM is a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. For this study an ISM is not required. However, at each site, and at the request of DMID, in real time, the local PI should be able to identify an independent physician to function as ad-hoc ISM. That person should have the privileges to examine the subject, review the subject medical and study record and provide an independent medical assessment and recommendation to DMID.

9.6.2. Data and Safety Monitoring Board (DSMB)

Safety oversight will be conducted by a DSMB that is an independent group of experts that monitors subject safety and advises DMID. The DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to the study. The DSMB will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial. The membership will include a chairperson and a statistician who are experienced in clinical trials conduct and have prior DSMB experience. The DSMB will review study progress and participant, clinical, safety, and immunogenicity data at the following time points: after 250, 500, and 750 individuals have been enrolled into the trial.

- Data review for enrollment feasibility and safety after 250 individuals are enrolled into the trial (interim review 1).

-
- Data review for enrollment feasibility, safety and futility after 500 and 750 individuals are enrolled into the trial (interim review 2 and 3, respectively).
 - Data review for safety at study specific time frames above; and at least annually.

Ad hoc reviews may be scheduled in response to an anticipated safety issue such as a halting rule being met, or by request of DMID. The DSMB will also have a final review meeting 6 to 8 months after clinical database lock to review the cumulative unblinded safety and efficacy data for the study. For the details of the interim reviews and analyses, consult Section 11.

The DSMB will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. Procedures for DSMB reviews/meetings will be defined in the charter. The DSMB will review applicable data to include, but not limited to, study progress and participant, clinical, safety, and immunogenicity data which may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing, protocol defined SAEs, and assays results. Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by group. The DSMB may also be provided with expected and observed rates of the liver function abnormalities in an unblinded fashion. The DSMB will meet and review this data at scheduled time points or ad hoc as needed during the study as defined in the protocol and DSMB charter. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with the study (as applicable), and to continue, modify, or terminate the study.

DMID or the DSMB chair may convene the DSMB on an ad hoc basis according to protocol criteria or if there are immediate concerns regarding observations during the course of the study. The DMID Medical Monitor is empowered to stop enrollment and dosing of the study drug if halting criteria are reported. The DMID Medical Monitor will be responsible for reviewing any protocol defined SAEs in real time. The DSMB will review safety events on a regular basis and ad hoc during the study.

10. CLINICAL MONITORING

Site monitoring is conducted to ensure that the human subject protections, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines and applicable regulations, and that the study is conducted in accordance with the protocol, protocol-specific MOP and applicable sponsor standard operating procedures. DMID, the sponsoring agency, or its designee will conduct site-monitoring visits as detailed in the clinical monitoring plan.

Site visits will be made at standard intervals as defined by DMID and may be made more frequently as directed by DMID. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, informed consent forms, medical and laboratory reports, and protocol and GCP compliance. Site monitors will have access to the study site, study personnel, and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with site principal investigators to discuss any problems and actions to be taken and document visit findings and discussions.

11. STATISTICAL CONSIDERATIONS

11.1. Study Hypotheses

The primary objective of the study is to assess the clinical response of early empiric antifungal therapy with fluconazole at Day 22 in subjects with coccidioidomycosis pneumonia.

The study is designed to test the following hypothesis in the primary efficacy analysis conducted in the cocci-positive per protocol analysis population (see Section 11.4.1):

Null hypothesis: “The proportion of subjects with coccidioidomycosis pneumonia with protocol-defined clinical response is the same in the cohort of subjects receiving fluconazole as compared to placebo.”

Alternative hypothesis: “The proportion of subjects with coccidioidomycosis pneumonia with protocol-defined clinical response is different in the cohort of subjects receiving fluconazole as compared to placebo.”

The study design and primary hypothesis is based on the following parameters supplied by subject matter experts:

- The composite score will be sensitive to changes in the course of disease as a result of empiric treatment with fluconazole.
- A 50% reduction in composite score is a clinically meaningful reduction which has been used as a measure of clinical response in other trials.
- A Day 22 time point will be optimal for measuring clinical response as compared to a longer time point because subjects in both study arms will eventually resolve disease,
- The proportion of subjects responding at Day 22 will be 0.20 and 0.40 in the placebo and fluconazole arms, respectively.

However, there is considerable uncertainty in the design parameters, as they are based on natural history studies, and this is the first randomized trial of empiric therapy with fluconazole for coccidioidomycosis. The most important contribution of this trial may be to confirm or refute these assumptions and set the stage for future trials.

Several of the secondary and exploratory objectives in the trial are focused on validating the sensitivity of the composite score, and its individual components, to intervention with fluconazole. This is motivated by Blair et al. (2014) who reported that subjects who received antifungal treatment had a reduced time to full attendance at work and reduced time to 50% improvement in SF-36 Physical Component Score [13].

11.2. Sample Size Considerations

11.2.1. Sample Size for Per Protocol Analysis Population

The primary analysis will compare the proportion of subjects achieving clinical response at Day 22 among efficacy evaluable subjects, defined as subjects in the Cocci-Positive Per Protocol analysis population who meet the case definition of coccidioidomycosis pneumonia who were compliant with the intervention administration and have coccidioidal serology data available at the Day 1 and 22 visits. We further assume that the clinical response proportion at Day 22 will be 0.20 in the placebo arm, and 0.40 in the fluconazole arm. As described in section 11.2.3, enrollment will continue until 200 subjects are evaluable for efficacy, 100 in each treatment arm, which suffices for 88% power for the Z test with unpooled variance to compare proportion of clinical responses at Day 22 at the two-sided level of 0.05. This is the primary sample size calculation which forms the basis for target enrollment to the study and for subsequent sample size re-estimation procedures at scheduled interim analyses while the study is enrolling.

A secondary analysis in the Cocci Positive Modified Intent-to-Treat population will compare the proportion of responders at Day 22, treating subjects dropping out before the Day 22 visit as non-responders. Assuming that the probability of drop-out before Day 22 is 20% among cocci-positive subjects, we would expect that 250 cocci-positive subjects would be available for this secondary analysis as a result of reaching the target sample size of 200 cocci-positive subjects with Day 22 follow-up for the primary analysis. Since subjects who drop-out are considered non-responders, the probability of response in the control-arm subjects would be $0.8 * 0.2 = 0.16$, and in the treated subjects would be $0.8 * 0.4 = 0.32$. The Z-test with unpooled variance has power of 85% to detect this difference in response proportions with 125 cocci-positive subjects per arm.

A secondary analysis in the Intent-to-Treat population will compare the proportion of responders at Day 22 between fluconazole and control arms in all randomized subjects, using a two-sided level .05 test of non-inferiority with a margin of an absolute difference of 0.05. Subjects who drop-out before Day 22 will be imputed as non-responders for cocci-positive subjects, and as responders for cocci-negative subjects. Assuming that an enrolled subject has a 20% chance of being cocci-positive, and that the probability of response is 20% among cocci-positive subjects receiving control, 40% for cocci-positive subjects receiving treatment, and 70% for cocci-negative subjects, then the probability that a control subject responds is given by $0.2*(0.8*0.2 + 0.2*0.0) + 0.8*(0.8*0.7 + 0.2*1.0) = 0.64$, and the probability that a treated subject responds is given by $0.2*(0.8*0.4 + 0.2*0.0) + 0.8*(0.8*0.7 + 0.2*1.0) = 0.672$. The non-inferiority test has power of 78% if 1,000 subjects are enrolled, and 86% if 1,250 subjects are enrolled.

The power calculations in this section were performed with PROC POWER in SAS 9.4 or in R.

11.2.2. Sensitivity of Sample Size to Assumptions

Table 5 displays the power of the Z test for different 22-day response proportions. In the power calculations, we have assumed that the absolute difference in true clinical response proportions is 0.20. If the effect size is larger than anticipated, power will be greater. If the effect size is less than 50%, power will be much lower. For example, if the true clinical response proportions are 0.20 and 0.30, power for the Z test drops to 37%. This situation could arise if the case definition of coccidioidomycosis pneumonia has lower specificity than expected. That is, per the protocol definition, some subjects who do not have coccidioidomycosis pneumonia are erroneously classified as cases.

This misclassification could result in an attenuated treatment effect. As displayed in Table 5, depending on the magnitude of the effect attenuation, power can be greatly affected.

Table 5: Power of the Z Test for Different Day 22 Response Rates

		Rate in Fluconazole Arm								
		0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Rate in Placebo Arm	0.1	5.0	50.8	94.8	100	100				
	0.2		5.0	37.1	87.6	99.6	100			
	0.3			5.0	31.6	82.8	99.2	100		
	0.4				5.0	29.4	81.2	99.2	100	
	0.5					5.0	29.4	82.8	99.6	100
	0.6						5.0	31.6	87.6	100
	0.7							5.0	37.1	94.8
	0.8								5.0	50.8
	0.9									5.0

In the power calculations, we have assumed that the clinical response proportion in the placebo arm is 0.20. If the effect size is maintained at 0.20, but the proportions are nearer to 0.50, power will be lower than reported, and if the proportions are farther from 0.50, power will be higher than reported. This is a result of the fact that the variance of a binomial distribution with probability of response p is given by $p*(1-p)$ which is maximized at $p = 0.50$.

The misclassification of coccidioidomycosis pneumonia described above could result in an attenuated treatment effect and/or attenuated arm-specific response proportions. The difficulty in predicting the magnitude of the misclassification or its effect on the power available for analyses highlights the importance of the alternate case definition analyses (Exploratory Objective 5). The primary analysis will be performed in the cocci-positive per-protocol population which excludes subjects who do not meet the primary case definition of coccidioidomycosis pneumonia. As denoted in Section 11.2.3 below, we estimate that a subset of the enrolled

population will be eligible for the cocci-positive per-protocol population. If the primary case definition does not adequately capture all subjects who truly have coccidioidomycosis pneumonia (i.e. has a high false-negative rate), two consequences are possible. First, the observed proportion of enrolled subjects that are eligible for the cocci-positive per-protocol population may be higher than our estimate. This possibility prompted the planned sample size assessment described in Section 11.3.3. Second, since a subset of all enrolled cocci-positive subjects would be included in the primary analysis, the observed treatment effect may be altered from the true treatment effect if the cocci-positive subjects who meet the primary case definition differ in any meaningful way from those cocci-positive subjects who do not meet the primary case definition. Again, this highlights the importance of the planned secondary analyses. The power calculations in this section were performed with PROC POWER in SAS 9.4.

11.2.3. Calculation of Target Enrollment

We estimate that 20% of the enrolled population will be eligible for the cocci-positive per protocol analysis population. Therefore, to reach the cocci-positive per protocol analysis population sample size of 200 subjects, it will be necessary to enroll at least 1,000 subjects to the study.

Since the assumptions underlying the sample size calculations are uncertain, a blinded re-assessment of sample size and target enrollment will be performed at an interim analysis while enrollment is ongoing. Refer to the next section on Planned Interim Analyses for a discussion.

11.3. Planned Interim Analyses

The following [Table 6](#) shows the planned schedule of DSMB review of the data. The DSMB will meet at minimum once per year and schedule ad hoc reviews as needed.

Table 6: Planned Interim Analysis Table

Analysis	Enrollment Target	Purpose of the Analyses
Interim 1	250	Safety Review and Enrollment Feasibility
Interim 2	500	Safety Review, Futility, and Enrollment Feasibility
Interim 3	750	Safety Review, Futility, and Enrollment Feasibility

Final DSMB review	1,000 6-8 months after data lock	Unblinded comprehensive review of cumulative safety and efficacy data for the study.
-------------------	--	--

11.3.1. Interim Safety Review

Interim safety review may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing, and SAEs as defined in Section 9.2.2. Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by group. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion. The DSMB will meet and review this data at scheduled time points or ad hoc as needed during the study as defined in the DSMB charter. As an outcome of each review/meeting, the DSMB will make a recommendation to DMID as to the advisability of proceeding with study enrollment and procedures (as applicable), and to continue, modify, or terminate the study.

Additionally, the study will be monitored to determine if any of the halting rules described in Section 9.5 are met.

11.3.2. Interim Immunogenicity or Efficacy Review

At the second and third interim analysis, the unblinded statistical team will calculate the probability conditional on the current trend in the accumulated data that the final analysis will show a benefit in favor of fluconazole. The DSMB will report to the sponsor only that the trial met the standard for continuation (conditional power above 5%). The sponsor will weigh the recommendation of the DSMB regarding futility and the separate blinded assessment of enrollment feasibility, and will decide whether to continue the trial, and if so, whether to increase the sample size, and by how much. It is recognized that statistical futility (low conditional power), and operational futility (unachievable enrollment targets), are closely related issues, and that this somewhat arbitrary distinction is being made to facilitate blinded decision making. The power calculations in Section 11.2.1 considered the power of the Z test for a fixed sample size and no interim analysis. A simulation study was performed to calculate the power available for the final analysis in a trial containing a futility analysis to be performed after 500 and 750 subjects have been enrolled and followed until Day 22. In this setting, uniform enrollment was also assumed.

At each futility analysis, the conditional power was calculated and if the conditional power was less than 5%, the trial was terminated. [Table 7](#) displays the power of the Z test for different Day 22 response rates resulting from the simulation study. Comparing these results with [Table 5](#) in

Section 11.2.2., there is minimal impact on power. If the true clinical response proportions are 0.20 and 0.40, the power drops slightly to 85.9%.

Table 7: Power of the Z Test for Different Day 22 Response Rates with a Futility Analysis

		Rate in Fluconazole Arm								
		0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Rate in Placebo Arm	0.1	4.8	48.7	93.9	99.8	100.0				
	0.2		4.7	34.9	85.9	99.1	100.0			
	0.3			4.7	30.1	80.8	98.6	100.0		
	0.4				5.0	27.7	78.7	98.6	100.0	
	0.5					4.8	28.0	80.5	99.1	100.0
	0.6						5.0	29.6	85.6	99.9
	0.7							4.7	34.8	94.0
	0.8								4.7	49.2
	0.9									4.8

Table 8 and Table 9 display the chance of deeming the trial futile and terminating the trial at the second and third interim analysis, respectively. The selection of a 5% threshold for futility appears to be reasonable as, if the protocol assumptions are correct, the chance of deeming the trial futile at the second and third interim analysis is 4.5% and 2.2%, respectively. This results in a 6.7% chance of terminating the trial early due to futility. Given that the stopping rule is conservative, there is a high chance of terminating the trial early at either interim analysis when there is no treatment benefit (e.g. if the true rates in both arms are both 0.2, the chances of futility are 42.0% and 30.0%, or a 72.0% chance of terminating the trial early due to futility).

Table 8: Chance of Futility at Second Interim Analysis

		Rate in Fluconazole Arm								
		0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Rate in Placebo Arm	0.1	42.6	16.7	2.1	0.1	0.0				
	0.2		42.0	23.1	4.5	0.4	0.0			
	0.3			41.5	26.0	6.2	0.6	0.0		
	0.4				41.8	27.1	7.2	0.6	0.0	
	0.5					42.3	26.5	6.5	0.4	0.0
	0.6						41.8	25.8	4.8	0.1

	0.7							41.5	23.5	2.0
	0.8								42.0	17.6
	0.9									42.6

Table 9: Chance of Futility at Third Interim Analysis

		Rate in Fluconazole Arm								
		0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Rate in Placebo Arm	0.1	29.8	11.1	0.9	0.0	0.0				
	0.2		30.0	15.2	2.2	0.1	0.0			
	0.3			31.0	16.8	3.2	0.2	0.0		
	0.4				30.7	17.7	3.2	0.1	0.0	
	0.5					30.9	18.1	3.4	0.1	0.0
	0.6						30.7	17.5	2.4	0.0
	0.7							31.0	15.7	0.7
	0.8								30.0	10.0
	0.9									29.8

11.3.3. Enrollment Feasibility

The planned interim assessments of enrollment feasibility will include a blinded re-assessment of sample size.

At each interim analysis the data for subjects who were enrolled at least 21 days prior to the data cut-off date for the DSMB report will be used to predict the number of subjects that will be evaluable for the per protocol analysis population at the time of the final analysis. If the predicted count for the number of subjects is less than 200, the enrollment target will be inflated sufficiently to reach this target.

It is acknowledged that this is a simplistic approach to sample size re-estimation which is impacted by the uncertainty in the rate estimates. It is also perforce limited in that a blinded analysis does not estimate the current treatment effect, but instead assumes it is equal to that proposed in the study design. This analysis is intended primarily to provide a framework to review the adequacy of the assumptions underlying the trial design and assess the operational feasibility of reaching the enrolment target, and to permit that discussion to take place amongst the blinded study team that is responsible for trial conduct and decision making.

The simulation study described in Section 11.3.2 was extended to assess the impact on the power available for the final analysis when sample size re-estimations as described above are included with the futility analyses at the second and third interim analyses. In the simulation study, multiple scenarios were considered which varied the following parameters:

The true rates of response in each arm (null and alternative hypothesis)

The percentage of subjects eligible for the cocci-positive per-protocol population (10% or 20%)
 The maximum allowable sample size of the trial (1500 or 1250)

Table 10 displays the power of the Z test, the average number of total subjects enrolled across the simulated trials, and the average enrollment target across the simulated trials for each of the scenarios.

Scenarios 1 and 4 correspond to the protocol specified alternative hypothesis in which the arm-specific Day 22 cumulative response is 0.40 and 0.20, and an assumed 20% of subjects are eligible for the per-protocol analysis. Comparing the adaptive design (Table 10) to the fixed sample size design (Table 5), there is little impact of adaption on either power or sample size. Scenarios 2 and 5 correspond to the protocol specified null hypothesis in which the arm-specific Day 22 cumulative response is 0.20 in both arms. In these scenarios, the type I error is preserved at < 5% and the average sample size is about 25% less than that of the fixed sample size of 1000. Scenarios 3 and 6 correspond to the protocol specified alternative hypothesis, but with only half as many subjects eligible for the per protocol analysis (10% versus 20%). In this setting power is increased from 56.9% without sample size re-estimation (not tabulated) to 69.8% or 64.4% corresponding to the limit of 1500 or 1250.

For comparison, if the arm-specific Day 22 cumulative response is 0.30 and 0.10 (attenuated response proportions with protocol-assumed effect size), and an assumed 20% of subjects are eligible for the cocci-positive per-protocol analysis, the power available is 94.7% (not displayed in Table 10). If the arm-specific Day 22 cumulative response is 0.35 and 0.20 (attenuated treatment effect), and an assumed 20% of subjects are eligible for the per-protocol analysis, the power available is 65.3% (not displayed in Table 10).

Table 10: Operating Characteristics of a Trial Design with Both a Futility and Sample Size Assessment at the Three Interim Analyses

Scenario	Power	Average Number of Subjects Enrolled	Average Accrual Goal
1, Fluconazole, Placebo Rates: 0.4, 0.2 Percentage of subjects eligible for cocci-positive PP: 20% Maximum Allowable Sample Size: 1500	87.1	1019	1046
2, Fluconazole, Placebo Rates: 0.2, 0.2 Percentage of subjects eligible for cocci-positive PP: 20% Maximum Allowable Sample Size: 1500	4.6	734	1026

3. Fluconazole, Placebo Rates: 0.4, 0.2 Percentage of subjects eligible for cocci-positive PP: 10% Maximum Allowable Sample Size: 1500	69.8	1336	1430
4. Fluconazole, Placebo Rates: 0.4, 0.2 Percentage of subjects eligible for cocci-positive PP: 20% Maximum Allowable Sample Size: 1250	87.0	1015	1044
5. Fluconazole, Placebo Rates: 0.2, 0.2 Percentage of subjects eligible for cocci-positive PP: 20% Maximum Allowable Sample Size: 1250	4.6	728	1025
6. Fluconazole, Placebo Rates: 0.4, 0.2 Percentage of subjects eligible for cocci-positive PP: 10% Maximum Allowable Sample Size: 1250	64.4	1120	1214

11.4. Final Analysis Plan

11.4.1. Analysis Populations

Safety Analyses:

- Safety population – This safety analysis population includes all subjects who took at least one dose of study medication.

Efficacy Analyses:

- Intent-to-Treat (ITT) population – This efficacy analysis population includes all randomized subjects.
- Cocci Positive Modified Intent-to-Treat (mITT) population – This efficacy analysis population includes all randomized subjects who meet the case definition of coccidioidomycosis pneumonia and took at least one dose of study medication. Note that it is not necessary for a subject to be adherent to study drug to be eligible for inclusion in the mITT population.
- All Randomized Modified Intent-to-Treat (mITT) population – This efficacy analysis population includes all randomized subjects who took at least one dose of study medication regardless of cocci-status. Note that it is not necessary for a subject to be adherent to study drug to be eligible for inclusion in the mITT population.

- Cocci Positive Per-Protocol (PP) population – This efficacy analysis population includes randomized subjects who meet the case definition of coccidioidomycosis pneumonia who were compliant with the intervention administration and have coccidioidal serology data available at the Day 1 and 22 visits.
- All Randomized Per-Protocol (PP) population – This efficacy analysis population includes randomized subjects who were compliant with the intervention administration regardless of cocci-status and have coccidioidal serology data available at the Day 1 and 22 visits.

Adherence is assessed at each study visit depending on the fraction of expected pills taken on or before that time point. If at any visit the subject's cumulative fraction of pills taken drops below 80%, they are deemed non-adherent. This decision is not reversible, even if the subject's cumulative fraction of pills taken rises above 80% at a future visit.

From that visit forward in time, the subject is dropped from the PP analysis populations, and their data after that visit is censored from time to event analysis, and they are dropped from any fixed time point analyses occurring after that visit. Data collected from time points prior to the time point at which a subject becomes non-compliant will still contribute to efficacy analyses. In the unlikely event of an error in randomization or drug distribution, subjects will be grouped by the study product they actually received in the per-protocol and safety analyses, but will be grouped by their intended randomized assignment in the intent-to-treat and modified intent-to-treat analysis.

11.4.2. Baseline Characteristics

Baseline and demographic characteristics will be summarized overall and by treatment group. For both continuous and categorical variables, appropriate summary statistics will be applied. For continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, minimum, and maximum. For categorical variables, descriptive statistics will include counts and percentages per category.

11.4.3. Safety Analysis Plan

Safety evaluations will be based on the incidence, severity, and type of clinically significant physical examination findings, clinically significant vital signs, and SAEs as defined in Section 9.2.2. Safety variables will be tabulated and presented for all subjects in the safety population, grouped by treatment group.

SAEs will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) for preferred term and system organ class. The rate and exact 95% confidence intervals of related SAEs in aggregate, and by MedDRA categories, will be computed. The number of SAEs will be reported by a detailed listing showing the type, MedDRA coding, relevant dates (administration and adverse event), severity, relatedness, and outcome for each event.

Laboratory toxicities will be analyzed by taking the most severe response over the follow-up period, dichotomizing into a binary variable (none or mild versus moderate or severe) and using exact confidence intervals to summarize the event and toxicity rates. Tabular and graphical summaries of events will be presented for each solicited symptom, by type, severity (none, mild, moderate, severe), and time point post-administration.

Laboratory and vital sign data will also be presented as change from baseline. Variable transformations will be applied as appropriate. Shift tables may be produced for select laboratory parameters.

11.4.4. Efficacy Analysis Plan

A separate statistical analysis plan document will be generated which will contain the details of the efficacy analyses. In this section below, the primary efficacy analysis is described and the secondary efficacy analyses are briefly outlined. The exploratory efficacy analyses will be addressed in the statistical analysis plan and are not described here.

11.4.4.1. Primary Efficacy Analysis

The primary efficacy analysis tests the difference between the fluconazole and placebo treatment groups in the proportion of subjects with an occurrence of clinical response at Day 22. Subjects without a clinical response at Day 22 will be coded as treatment failures while subjects with a clinical response at Day 22 will be coded as an observed event if the clinical response outcome measure definition (Section 3.2.1) is met.

A test of difference between the proportion of clinical responses in the fluconazole and placebo groups at the Day 22 time point will be performed using the Z test. The use of this test statistic will permit us to use the method of B-values to calculate conditional power of the test in the planned futility analyses, as outlined in “Statistical Monitoring of Clinical Trials, a Unified Approach”, by Proschan et al [22]. Details of this procedure will be provided in the statistical analysis plan.

The primary efficacy analysis will be performed in the cocci-positive per protocol analysis population. Secondary analyses will be performed in the all randomized per protocol population, all randomized and cocci-positive ITT and the mITT populations (see also Secondary Objectives 1 and 6). Sensitivity analyses, which will assess the impact of drop-out, censoring mechanisms, and analysis methods on the primary analysis, may be performed. These analyses will be specified in the separate statistical analysis plan document.

In addition to the planned tests of hypotheses, descriptive analyses will be performed for the primary endpoint. The number of clinical responses observed will be tabulated by time point, including and beyond Day 22, and treatment group. Tabular and graphical summaries will be prepared for the composite MSG score across all assessment time points.

To investigate whether there is evidence of a differential diagnosis of coccidioidomycosis between treatment arms, which might result in selection bias for inclusion in our primary analysis, the number of coccidioidomycosis cases in each treatment arm will be compared among all randomized subjects.

11.4.4.2. Secondary Efficacy Analyses

Table 11 below briefly outlines the analytic approaches that will be taken for the secondary efficacy analyses. Details of the analyses will be described in the separate statistical analysis plan document.

Table 11: Secondary Efficacy Analyses

Secondary Objective	Outcome Measure	Main Analytic Strategy
(SO 1): To assess the clinical response of early empiric antifungal therapy with fluconazole at Day 22 in subjects with coccidioidomycosis pneumonia regardless of adherence with the study intervention.	Proportion of clinical response at Day 22 regardless of adherence to the study intervention in each treatment group.	Repeat the primary efficacy analyses in the all randomized mITT, cocci-positive mITT, and ITT populations.
(SO 2): To assess the clinical response of early empiric antifungal therapy with fluconazole at Day 43 in subjects with coccidioidomycosis pneumonia regardless to adherence with the study intervention.	Proportion of clinical response at Day 43 regardless of adherence to the study intervention in each treatment group.	Repeat the analyses for SO 1 using Day 43 as the time point for the outcome measure instead of Day 22 as well as perform a time-to-event analysis. This analysis will be performed in the all-randomized mITT, cocci-positive mITT, and ITT populations.

<p>(SO 3): To compare the clinical response and its individual components by study group, over time, in subjects with coccidioidomycosis pneumonia.</p>	<p>The mean, median, and quartiles of the FLEET CAP score at Days 22, 29 and 43 in each treatment group.</p> <p>The mean, median, and quartiles for each component of the FLEET CAP score at Days 22, 29 and 43 in each treatment group.</p> <ol style="list-style-type: none"> 1. Cough 2. Fatigue 3. Chest Pain 4. Dyspnea (Shortness of breath) 5. Sputum production 6. Night Sweats 7. Fever 8. Hypoxia 	<p>Descriptive and/or graphical summaries of the outcome measures by treatment group. This analysis will be performed in both PP populations, both mITT populations, and the ITT population.</p>
<p>(SO 4): To assess the impact of early empiric antifungal therapy with fluconazole on days lost from work or school and responses to the SF-12v2 and PROMIS Item Bank v2.0 - Ability to Participate in Social Roles and Activities - Short Form 4a in subjects with coccidioidomycosis pneumonia.</p>	<p>Number of days of school or work missed after the start of the treatment through Day 43 in each treatment group.</p> <p>The mean, median, and quartiles for the mental component summary (MCS) and physical component summary (PCS) scores of the SF-12v2 instrument and the responses to the individual items of the PROMIS Item Bank v2.0 - Ability to Participate in Social Roles and Activities - Short Form 4a at Days 22, 43, 90 and 180 in each treatment group.</p>	<p>Descriptive and/or graphical summaries of the outcome measures by treatment group. This analysis will be performed in both PP populations, both mITT populations, and the ITT population.</p>

<p>(SO 5): To assess the effect of early empiric antifungal therapy with fluconazole through Day 43 in subjects with coccidioidomycosis pneumonia on all-cause mortality by treatment group.</p>	<p>Incidence rate of all-cause mortality after the start of treatment and through Day 43 by treatment group.</p>	<p>Descriptive summaries of the outcome measure by treatment group. This will be performed in both PP populations, both mITT populations, and the ITT analysis population.</p>
<p>(SO 6): To assess whether early empiric antifungal therapy with fluconazole at Day 22 is non-inferior to placebo as defined by clinical response at Day 22 in all randomized subjects, regardless of coccidioidomycosis pneumonia status or adherence with study intervention, with baseline and follow-up FLEET-CAP scores.</p>	<p>Proportion of clinical response at Day 22 among all randomized subjects, regardless of coccidioidomycosis status or adherence with study drug, in each treatment group.</p>	<p>Two-sided level .05 test of non-inferiority based on whether the 95% confidence interval for the difference in estimates of 22-day response proportions excludes an absolute difference of .05 in favor of the placebo arm. This analysis will be performed in the ITT population.</p>

11.4.4.3. Exploratory Efficacy Analyses

The exploratory efficacy analyses will be described in the separate statistical analysis plan document.

12. 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. Each participating site will permit authorized representatives of the DMID, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical study records for the purposes of quality assurance reviews, audits, monitoring and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, ECG, 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. 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.

13. QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, the participating site is responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The site principal investigator will provide direct access to all trial-related sites, source data/data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The site principal investigator will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The SDCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

14. ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1. Ethical Standard

The site principal investigator will ensure that this trial is conducted in full conformity with principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR 46, 21 CFR 50 and 56, and ICH E6; 62 Federal Regulations 25691 (1997), if applicable. The site principal investigator's Institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research.

14.2. Institutional Review Board

Prior to enrollment of subjects into this trial, the approved protocol and informed consent form(s) will be reviewed and approved by the appropriate IRB.

IRB approval is required for subject recruitment materials and procedures, and any other materials provided to subjects, such as summaries, pamphlets, videos, instructions, etc., prior to enrolling any subjects on the study.

The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial and a copy will be provided to DMID. The IRB Federal Wide Assurance number will be provided to DMID. Only the registered IRB listed on the institution's Federal Wide Assurance (FWA), issued by the Office of Human Research Protection (OHRP), are authorized to review and approve these documents.

Should amendments to the protocol be required, the amendments will be written by the Sponsor and provided to the site principal investigator for submission to the IRB at the address listed below:

DUHS IRB Office
Hock Plaza
Suite 405
2424 Erwin Road
Campus Box 2712
Durham, NC 27705
Phone: (919) 668-5111
Fax: (919) 668-5125

In addition to submission to the Duke IRB, amendments will also be approved by the participating institution's IRB. Any amendments to the protocol consent materials or other study documentation as referenced above must be approved by the participating institution's IRB

before they are implemented, unless the change was made for the immediate safety of the subject(s).

14.3. Informed Consent Process

Before any study procedures are performed, subjects must sign an informed consent form that complies with the requirements of 21 CFR Part 50 and 45 CFR 46 and the local IRB.

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, subjects will receive a comprehensive explanation of the proposed study procedures and study interventions/products, including the nature and risks of the trial, alternate therapies, any known AEs, the investigational status of the components, and the other elements that are part of obtaining proper informed consent. Subjects will also receive a detailed explanation of the proposed use and disclosure of their protected health information, including specifically their serum samples. Subjects will be allowed sufficient time to consider participation in the trial, after having the nature and risks of the trial explained to them, and have the opportunity to discuss the trial with their family, friends or legally authorized representative or think about it prior to agreeing to participate.

Informed consent forms describing in detail the study interventions/products, study procedures, risks and possible benefits are given to subjects. The informed consent form must not include any exculpatory statements. Informed consent forms will be IRB-approved and subjects will be asked to read and review the appropriate document. Upon reviewing the appropriate document, the site principal investigator (or designee) will explain the research study to subjects and answer any questions that may arise. Subjects must sign the informed consent form, and written documentation of the informed consent process is required prior to starting any study procedures/interventions being done specifically for the trial, including administering study product.

DMID will provide the site principal investigator, in writing, any new information that significantly impacts the subjects' risk of receiving the investigational product. This new information will be communicated by the site principal investigator to subjects who consent to participate in the trial in accordance with IRB requirements. The informed consent document will be updated and subjects will be re-consented per IRB requirements, if necessary.

Study personnel may employ recruitment efforts prior to obtaining study consent if a patient-specific screening consent is on record or if the IRB has agreed that chart review is allowed without a fully executed screening consent. In cases where there is not a patient-specific screening consent on record, site clinical staff may pre-screen via chart review and refer potential subjects to the research staff. Research staff would obtain written consent per the standard informed consent process before conducting protocol-specific screening activities.

Subjects will be given a copy of all informed consent forms that they sign.

By signing the informed consent form, subjects agree to complete all evaluations required by the trial, unless the subject withdraws voluntarily, or is withdrawn or terminated from the trial for any reason.

The rights and welfare of subjects will be protected by emphasizing to subjects that the quality of their medical care will not be adversely affected if they decline to participate in or withdraw from this trial.

14.3.1. Informed Consent/Assent Process (in Case of a Minor)

N/A

14.4. Exclusion of Women, Minorities, and Children (Special Populations)

This trial will be inclusive of all adults who meet the Subject Inclusion/Exclusion Criteria, regardless of religion, sex, or ethnic background. Should the outcome of this trial be deemed acceptable, additional trials may be initiated in other populations.

Children under the age of 18 will not be included in this trial as presently there are no efficacy data in adults.

14.5. Subject Confidentiality

Subjects will be assigned code numbers and will not be identified by name. Subject confidentiality is strictly held in trust by the participating site principal investigators, their study personnel, the sponsor(s), and their agents. This confidentiality is extended to cover testing of biological samples, 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 trial or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All information provided by the Sponsor and all data and information generated by the participating site as part of the trial (other than a subject's medical records) will be kept confidential by the site principal investigator and other study personnel to the extent permitted by law. This information and data will not be used by the site principal investigator or other study personnel for any purpose other than conducting the trial. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the site principal investigator or other study personnel; (2) information which is necessary to disclose in confidence to an IRB solely for the evaluation of the trial (3) information which is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in Section 16. If a written contract for the conduct of the trial which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

The study monitor, applicable regulatory authorities, such as the FDA, or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the site principal investigator. This includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this trial. The participating sites will permit access to such records.

14.6. Study Discontinuation

If the trial is discontinued, subjects who sign the informed consent form, and are randomized and given study drug will continue to be followed for safety assessments.

14.7. Costs, Subject Compensation, and Research Related Injuries

There is no cost to subjects for taking part in this trial.

Subjects may be compensated for their participation in this trial. Compensation will be in accordance with the local IRB's policies and procedures, and subject to IRB approval.

If it is determined by the participating site and the site principal investigator that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject. Study personnel will try to reduce, control, and treat any complications from this trial. Immediate medical treatment may be provided by the participating site, such as giving emergency medications to stop immediate allergic reactions to the study drug. No financial compensation will be provided to the subject by the participating site for any injury suffered due to participation in this trial.

14.8. Future Use of Stored Specimens and Data

Subjects will be asked for permission to keep any samples taken specifically for future use and remaining samples for possible use in future research studies. Some examples of possible studies include examining additional immunological assessments for coccidioidomycosis or testing for antibodies against other viruses or bacteria. The samples will be stored indefinitely at an NIH-designated facility.

DMID will have a process in place to evaluate requests for use of those samples. Samples will be released to researchers or other institutions after NIH and appropriate Ethics Committee review and approvals are obtained. The samples will not be sold or used directly for production of any commercial product. Each sample will be encoded (labeled) only with a barcode and a unique tracking number to protect subject's confidentiality.

If future use requests is outside the consent for the initial study, e.g. human genetic testing, all subjects must be contacted again, and under an IRB approve protocol and consent, specifically and positively agree to such use of the future use samples. Without a specific consent from the study subjects no sample will be used for human genetic testing. If the subject refuses to be

contacted again (see Section 14.9) no human genetic testing can be performed on the future use or remaining samples.

There are no benefits to subjects in the collection, storage and subsequent research use of specimens. Results and incidental findings will not be shared with subjects or the subject's health care providers.

Subjects may be given the option to decide if they want their samples to be used for future research or have their samples destroyed at the end of the trial. The subject's decision can be changed at any time by notifying the study doctors or nurses in writing, and the unused identifiable samples will be destroyed. However, if the subject originally consents to future use and subsequently changes his/her decision, any data obtained prior to the withdrawal of consent may still be used for research.

Subjects will be given the option to decide if they want their identifiable (coded) data to be used for future or secondary-use research. The subject's decision can be changed at any time by notifying the study doctors or nurses in writing. The study team will then alert the NIH of the subject's decision to withdraw. No further identifiable data will be released after the consent is withdrawn. Any data released for research prior to the withdrawal of consent may still be used for the designated-research. Data that is no longer identifiable cannot be retrieved.

14.9. Permission to Be Contacted for Future Studies

Subjects will be given an option whether they give permission to be contacted for future studies for coccidioidomycosis. Subjects who agree to be contacted will have their name, address, and contact information entered into an institutionally-approved database with limited access and a password-encrypted system. The subject's name and contact information will not have health information, but will contain a code that may connect to data in this study's database. The subject may withdraw the permission to be contacted at any time by notifying the study staff in writing, and subsequently contact information will be removed from the database permanently. The new study's consent form will describe all aspects of the new study, the extent of the subject's information released from this study, and the extent of confidentiality.

If the subject refuses to be contacted again no human genetic testing can be performed on the future use samples.

15. DATA HANDLING AND RECORD KEEPING

15.1. Data Management Responsibilities

Data management will be the responsibility of the SDCC (the Emmes Corporation). All source documents and laboratory reports will be reviewed for accuracy and completeness by the clinical team. AEs will be graded, assessed for severity and causality, and reviewed by the site PI. Data collection is the responsibility of the clinical trial staff at the sites under the supervision of the PI. During the study, the principal investigator will maintain complete and accurate documentation for the study.

15.2. Data Capture Methods

Clinical (including, but not limited to, SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory values), reactogenicity, and immunogenicity data will be entered into a 21 CFR 11-compliant Internet Data Entry System provided by the SDCC. 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 data collection forms completed by the study personnel.

15.3. Types of Data

Data for this study will include clinical, safety, and outcome measures (e.g., clinical assessment findings, laboratory values, and immunogenicity data).

15.4. Timing/Reports

A final report will be prepared following the availability of all the safety, reactogenicity, and immunogenicity data. Interim statistical reports may be generated as deemed necessary and appropriate by DMID. Safety and immunogenicity summary reports may be generated for the DSMB.

After full analysis and final reporting is complete, and upon request and DMID approval, the SDCC will provide the participating sites with a summary of results by treatment group and/or subject treatment assignments. In this regard, the participating sites requesting such information to share with study subjects must do so in compliance with their respective IRB guidelines.

15.5. Study Records Retention

Study records and reports, including, but not limited to, case report forms (CRFs), source documents, informed consent forms (except for future use informed consent forms), laboratory test results, and medication inventory records, shall be retained for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has

been so notified; or longer according to institutional requirements. The site must contact DMID for authorization prior to the destruction of any study records. Informed consent forms for future use will be maintained as long as the sample exists.

15.6. Protocol Deviations

A protocol deviation is any noncompliance with the study protocol, GCP, or protocol-specific MOP requirements. The noncompliance may be either on the part of the subject, the site principal investigator, or other study personnel. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1
- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2

It is the responsibility of the site principal investigator and other study personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID, via the SDCC's AdvantageEDC. All protocol deviations, as defined above, must be addressed in study subject data collection forms. A completed copy of the DMID Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart. Protocol deviations must be sent to the local IRB/IEC per its guidelines. The site principal investigator and other study personnel are responsible for knowing and adhering to their IRB requirements.

16. PUBLICATION POLICY

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central (<http://www.ncbi.nlm.nih.gov/pmc/>) an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

- NIH Public Access Policy, <http://publicaccess.nih.gov/>
- NIH OER Grants and Funding, <http://grants.nih.gov/grants/oer.htm>

Following completion of the study, the lead principal 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 [23]. Other biomedical journals are considering adopting similar policies.

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. Results of any exploratory immunogenicity analysis will not be published prior to publication of the primary immunogenicity results for this study.

It is the responsibility of DMID to register this trial in an acceptable registry. Any clinical trial starting enrollment after 01 July 2005 must be registered on or before subject 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. For trials in which DMID is not the IND/IDE sponsor, or there is no IND/IDE, and DMID does not provide data management services, it is the responsibility of the investigator to register the trial and post results in compliance with Public Law 110-85, the Food and Drug Administration Amendments Act of 2007 (FDAAA).

Refer to:

- Public Law 110-85, Section 801, Clinical Trial Databases

17. LITERATURE REFERENCES

- [1] Valley Fever in People. Valley Fever Center for Excellence website. <https://www.vfce.arizona.edu/ValleyFeverInPeople/>. Accessed August 6, 2015.
- [2] Fungal pneumonia: a silent epidemic – Coccidioidomycosis (valley fever). Centers for Disease Control and Prevention website. <http://www.cdc.gov/fungal/pdf/cocci-fact-sheet-sw-us-508c.pdf>. Updated December 2012. Accessed August 6, 2015.
- [3] Blair JE, Chang YH, Cheng M, Vasvar LT, Vikram HR, Orenstein R, et al. Characteristics of Patients with Mild to Moderate Primary Pulmonary Coccidioidomycosis. *Emerg Infect Dis*. 2014 Jun;20(6):983-990. doi: 10.3201/eid2006.131842.
- [4] Valley Fever 2013 Annual Report. Office of Infectious Disease Services, Bureau of Epidemiology and Disease Control, Arizona Department of Health Services. <http://www.azdhs.gov/phs/oids/epi/valley-fever/documents/reports/valley-fever-2013.pdf>. Accessed February 2015.
- [5] Tsang CA, Anderson SM, Imholte SB, Erhart LM, Chen S, Park BJ, et al. Enhanced surveillance of coccidioidomycosis, Arizona, USA, 2007-2008. *Emerg Infect Dis*. 2010 Nov;16(11):1738-44. doi: 10.3201/eid1611.100475.
- [6] Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *N Engl J Med*. 2015 Jul 30;373(5):415-27. doi: 10.1056/NEJMoa1500245.
- [7] Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007 Mar 1;44 Suppl 2:S27-72.
- [8] Ohtani H, Taninaka C, Hanada E, Kotaki H, Sato H, Sawada Y, et al. Comparative pharmacodynamic analysis of Q-T interval prolongation induced by the macrolides clarithromycin, roxithromycin, and azithromycin in rats. *Antimicrob Agents Chemother*. 2000 Oct;44(10):2630-7.
- [9] Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med*. 2012 May 17;366(20):1881-90. doi: 10.1056/NEJMoa1003833.
- [10] Zeuli JD, Wilson JW, Estes LL. Effect of combined fluoroquinolone and azole use on QT prolongation in hematology patients. *Antimicrob Agents Chemother*. 2013 Mar;57(3):1121-7. doi: 10.1128/AAC.00958-12.
- [11] Nix DE. Cardiotoxicity Induced by Antifungal Drugs. *Current Fungal Infection Reports*. 2014;8(2):129-138.
- [12] Anstead GM, Graybill JR. Coccidioidomycosis. *Infect Dis Clin North Am*. 2006 Sep;20(3):621-43.

-
- [13] Blair JE, Chang YH, Cheng M, Vasvar LT, Vikram HR, Orenstein R, et al. Characteristics of Patients with Mild to Moderate Primary Pulmonary Coccidioidomycosis. *Emerg Infect Dis*. 2014 Jun;20(6):983-990. doi: 10.3201/eid2006.131842.
- [14] Catanzaro A, Galgiani JN, Levine BE, Sharkey-Mathis PK, Fierer J, Stevens DA, et al. Fluconazole in the treatment of chronic pulmonary and nonmeningeal disseminated coccidioidomycosis. NIAID Mycoses Study Group. *Am J Med*. 1995 Mar;98(3):249-56.
- [15] Galgiani JN, Catanzaro A, Cloud GA, Higgs J, Friedman BA, Larsen RA, et al. Fluconazole therapy for coccidioidal meningitis. The NIAID-Mycoses Study Group. *Ann Intern Med*. 1993 Jul 1;119(1):28-35.
- [16] Galgiani JN, Catanzaro A, Cloud GA, Johnson RH, Williams PL, Mirels LF, et al. Comparison of oral fluconazole and itraconazole for progressive, nonmeningeal coccidioidomycosis. A randomized, double-blind trial. Mycoses Study Group. *Ann Intern Med*. 2000 Nov 7;133(9):676-86.
- [17] Graybill JR, Stevens DA, Galgiani JN, Dismukes WE, Cloud GA. Itraconazole treatment of coccidioidomycosis. NIAID Mycoses Study Group. *Am J Med*. 1990 Sep;89(3):282-90.
- [18] Leidy NK, Rennard SI, Schmier J, Jones MK, Goldman M. The breathlessness, cough, and sputum scale: the development of empirically based guidelines for interpretation. *Chest*. 2003 Dec;124(6):2182-91.
- [19] Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. 1989 Oct;46(10):1121-3.
- [20] Klein JP, Logan B, Harhoff M, Andersen PK. Analyzing survival curves at a fixed point in time. *Stat Med*. 2007 Oct 30;26(24):4505-19.
- [21] Lin DY, Shen L, Ying Z, Breslow NE. Group sequential designs for monitoring survival probabilities. *Biometrics*. 1996 Sep;52(3):1033-41.
- [22] Proschan MA, Lan KKG, Wittes JT. *Statistical Monitoring of Clinical Trials: A Unified Approach*. New York: Springer-Verlag New York; 2006. 268 p.
- [23] De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *N Engl J Med*. 2004 Sep 16;351(12):1250-1.

18. SUPPLEMENTS/APPENDICES

APPENDIX A. SCHEDULE OF EVENTS

Table 12: Schedule of Study Procedures and Evaluations

Study Visit Number	V 01 [#]	V 02 [#]	V 03 [#]	V 04 [#]	V 05 [^]	V 06 ^{^^}	V 07 ^{^^}	Early Termination or Unscheduled Visit
Study Day	Day 1	Day 22	Day 29	Day 43	Day 49	Day 90	Day 180	
	-	-2d to +1d	-2d to +1d	-1d to +3d	-1d to +2d	±7d	±7d	
Obtain Informed Consent [∞]	X							
Collect Demographics and Employment/School Enrollment Status	X							
Review Eligibility Criteria	X	X	X					
Medical Record Review	X	X	X	X		X	X	X
Concomitant Medications	X	X	X	X				X ^d
Obtain Medical History [@]	X	X	X	X				X ^d
Vital Signs (Temp, BP, Pulse, Resp, O ₂ Sat, Weight)	X	X	X	X				X ^d
Height	X							
Resting 12-Lead ECG	X ^ζ							X ^c
Physical Examination ^a	X ^ζ	X	X	X				X ^d
FLEET CAP score	X	X	X	X				X ^d
Extra-Pulmonary Symptom Score	X	X	X	X		X	X	X
SF-12v2	X	X	X	X		X	X	X
PROMIS Short Form								
Days Missed from School or Work		X	X	X				X ^d
Pregnancy Test [%]	X	X	X	X				X ^d
Venous Blood Collection for Safety Labs [*]	X ^ζ	X	X	X				X ^d
POC HIV-1 Antibody Test	X							

Study Visit Number	V 01 [#]	V 02 [#]	V 03 [#]	V 04 [#]	V 05 [^]	V 06 ^{^^}	V 07 ^{^^}	Early Termination or Unscheduled Visit
Study Day	Day 1	Day 22	Day 29	Day 43	Day 49	Day 90	Day 180	
	-	-2d to +1d	-2d to +1d	-1d to +3d	-1d to +2d	±7d	±7d	
Venous Blood Collection for Coccidioidal serologies	X	X	X	X				X ^d
Future Use Samples: Blood ^{&}	X	X	X	X				X ^d
Future Use Samples: Urine, Nasopharyngeal Swab, and Throat Swab ^{&}	X							
Enroll/Randomize	X							
Dispense Study Product	X	X						
Obtain Cocci Status				X ^{SS}				
Reveal Treatment Status				X ^{SS}				X ^{d,SS}
Pill Count and Adherence Interview		X	X	X				X ^d
Therapeutic Drug Monitoring (Fluconazole)		X		X				X ^d
SAE Assessment	X	X	X	X	X			X ^d
Refer to Health Care Provider for Follow-Up ^b				X	X			X ^d

[∞]Prior to study procedures

^aClinician must be licensed to make medical diagnoses. Full examination to be performed on Day 1, thereafter, perform a targeted physical examination if indicated based on review of complete medical history.

^bReferrals to health care provider can be made at various time points. See study schedule for details.

^cIf termination occurs prior to Day 15

^dIf termination occurs prior to Day 43

[@]Complete medical history by medical record review and interview of subjects to be obtained on Day 1 and interim medical history by interview and medical record review of subjects to be obtained at follow-up visits.

[#]Indicates visits during blinded phase where the schedule is the same for all participants (all In Person)

^{*}Includes Hepatic function panel (AST, ALT, alkaline phosphatase and total bilirubin), BUN, Creatinine

[^]Safety follow up for those randomized to fluconazole.

^{^^} Follow-up (phone call) for all subjects who meet the protocol defined case definition as coccidioidomycosis positive. Patient reported outcomes (SF-12v2, PROMIS short form) and Extra-Pulmonary Symptom Scores will be performed but FLEET-CAP will not.

^{SS}Revealing the subject's treatment status and disease status should be done only after all study related assessments are completed. Disease status will be revealed if known based on review of available serologies.

[%]Urine for early termination. Serum or urine for all other visits. Only required for women of childbearing potential.

[&]Only required for subjects that have consented to additional sample collection for future use.

[§] For patients referred to study with existing standard of care safety labs, physical exam, and/or ECG within the past 72 hours and are available to the study team at the time of screening, these SOC activities can serve as the screening activities and do not require repeating. (laboratory tests are required to have the same normal range as the study site).