A Phase IIa Efficacy, Safety, Tolerability and Pharmacokinetic Study of Encochleated Amphotericin B (CAMB) in Patients with Mucocutaneous (Esophogeal, Oropharyngeal, Vulvovaginal) Candidiasis Who are Refractory or Intolerant to Standard Non- Intravenous Therapies

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Statement of Compliance

The trial will be carried out in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

NIH-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

List of Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AMB	Amphotericin B
APECED	Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy
AST	Aspartate Transaminase
AUC	Area Under the Concentration vs. Time Curve
AUC_{0-24}	Area Under the Concentration vs. Time Curve from Time Zero to 24 Hours Postdose
BID	Twice Daily
CAMB	Cochleate Oral Amphotericin B
CFR	Code Of Federal Regulations
C_{max}	Maximum Plasma Concentration
CMC	Chronic Mucocutaneous Candidiasis
CRF	Case Report Form
CRP	C-Reactive Protein
CRIMSON	Clinical Research Information Management System of the NIAID
DAMB	Deoxycholate Solubilized Amphotericin B
DCR	Division of Clinical Research

DSMB	Data and Safety Monitoring Board
EC	Esophageal Candidiasis
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
HRPP	Human Research Protection Program
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug
IP	Intraperitoneal
IRB	Institutional Review Board
IUD	Intrauterine Device
LCIM	Laboratory of Clinical Immunology and Microbiology
LC/MS-MS	Liquid Chromatography with Tandem Mass Spectrometry
MedRA	Medical Dictionary for Regulatory Activities
MFC	Minimum Fungicidal Concentration
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
OHRP	Office for Human Research Protections
OMC	Onychomycosis
OPC	Oropharyngeal Candidiasis
PBMC	Peripheral blood mononuclear cell
PI	Principal Investigator
PK	Pharmacokinetic(s)
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
SAE	Serious Adverse Event/Serious Adverse Experience
SD	Standard Deviation
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operation Procedure
$T_{1/2}$	Elimination half-life
T_{max}	Time to Reach Maximum Plasma Concentration
UP	Unanticipated Problem
VVC	Vulvovaginal Candidiasis
λZ	Apparent Elimination Rate Constant

Protocol Summary

Full Title:	A Phase IIa Efficacy, Safety, Tolerability and Pharmacokinetic Study of Encochleated Amphotericin B (CAMB) in Patients with Mucocutaneous (Esophogeal, Oropharyngeal, Vulvovaginal) Candidiasis Who are Refractory or Intolerant to Standard Non-Intravenous Therapies
Short Title:	CAMB for CMC
Clinical Phase:	**IIa**
IND Sponsor:	Matinas BioPharma Nanotechnologies, Inc.
Conducted by:	NIAID/LCIM
Principal Investigator:	Alexandra Freeman, MD
Sample Size:	N = 16
Accrual Ceiling:	**20**
Study Population:	Patients aged 18 to 75 years with mucocutaneous candidiasis (esophageal, oropharyngeal, or vulvovaginal) who are refractory or intolerant to standard non-intravenous therapies. Pregnant patients will be excluded.
Accrual Period:	**Closed to Enrollment**
Study Design:	This is an open-label, dose-titration trial to study the efficacy, safety, and pharmacokinetics of oral cochleate amphotericin B (CAMB) in the treatment of mucocutaneous candidiasis infections in patients who are refractory or intolerant to standard non-intravenous therapies.
Study Duration:	60 months. Individual patient participation will last for 1-2 months, with the possibility for continuation of up to 60 months.
Study Agent:	CAMB
Intervention Description:	CAMB will be administered orally at 200 mg/day (100 mg BID). If there is a clinical response after

2 weeks, then treatment will be extended for 2 more weeks. If there is no clinical response but study drug is tolerated, then doses will be escalated to 400 mg/day (200 mg BID). If after escalation there is a clinical response after 2 weeks, then treatment will be extended for 2 more weeks. If there is no clinical response and study drug is tolerated, then dose can be escalated again to 800 mg/day (400 mg BID) for an additional 2 weeks. If there is no clinical response after 2 weeks, the study drug will be discontinued. If there is clinical response after two weeks treatment will be extended for 2 more weeks. Participants have the option to enroll in the Extension phase of the study after achieving clinical response after 2 weeks at the highest tolerated dose of study drug.

Primary Objective: To assess the clinical response to treatment of mucocutaneous candidiasis (oropharyngeal candidiasis (OPC), esophageal candidiasis (EC), vulvovaginal candidiasis (VVC)) infections in patients who are refractory or intolerant to standard non-intravenous therapies after treatment for 14-days with the highest titrated dosage (Target Dosage) of CAMB per patient.

Secondary Objectives:
1. To assess the plasma, urine, and salivary PK of AMB after a single dose and after multiple doses (14 days) for both the starting dosage and subsequent up-titrations
2. To assess the safety and tolerability of CAMB in OPC, EC, and VVC
3. To assess mycological response in OPC, EC, and VVC

Exploratory Objective:
1. To assess the stool and vaginal secretion PK of AMB after a single dose and after multiple doses (14 days) for both the starting dosage and subsequent up-titrations.
2. To assess clinical response in those patients with a concomitant diagnosis of OMC.
3. To assess the safety and efficacy of long-term treatment (up to 60 months) with CAMB.

Primary Endpoints: Percentage of patients with a primary diagnosis of OPC, EC, or VVC who achieve Clinical Responder status after 14 days of treatment at the highest titrated CAMB dosage per patient (Target Dosage).

Secondary Endpoints:
1. Plasma, urine, and salivary single-dose and steady-state PK parameters and disposition of oral CAMB
2. Dose linearity/proportionality of oral CAMB with titration
3. Clinical Responder status after 28 days at the Target Dosage
4. Clinical Responder status after 14 days at each dosage level
5. Mycological response after treatment for 14 days and 28 days with the Target Dosage
6. Mycological response after treatment with each dosage level for 14 days
7. Rate of treatment-limiting toxicity
8. Rate of clinical relapse
9. Incidence of nephrotoxicity
10. Incidence of hypokalemia
11. Incidence of adverse events (AEs)
12. Clinical Responder status after 14 days of treatment at the Target Dosage per patient of a secondary, less severe candida infection

Exploratory Endpoints:
1. Stool and vaginal secretion single-dose and steady-state PK parameters and disposition of oral CAMB.
2. Clinical response in those patients with a concomitant diagnosis of OMC.
3. Long-term (up to 60 months) safety and efficacy.

Précis

Current therapeutic options for mucocutaneous candidiasis infections are limited. Azole antifungals are available in oral formulations and are typically well tolerated, but resistance can develop, and toxicities that occur with prolonged use include hepatotoxicity, fluoride toxicity, and photosensitivity (with voriconazole). Echinocandins (eg, caspofungin and micafungin) are very well tolerated but are only available as intravenous formulations and resistance has developed. Amphotericin derivatives are used for their broad fungicidal activity, but they require parenteral administration and have significant side effects such as nephrotoxicity that worsens with longer courses of treatment. Amphotericin administered as an oral solution is not widely available, is not very effective, and irritates the oral and esophageal tissues.

Our clinical group currently follows many patients with mucocutaneous candidiasis, some of whom have become resistant or intolerant to oral or standard treatment. We plan to treat these individuals with cochleated oral amphotericin B (CAMB) in order to clear their infections. We will monitor for safety and pharmacokinetics of CAMB and will follow markers of treatment response of fungal infection.

1 Background Information and Scientific Rationale

1.1 Background Information

1.1.1 Description of the Study Agent

Cochleate oral amphotericin B (CAMB) is a lipid-crystal, nano-particle formulation designed for targeted oral delivery of the antifungal drug amphotericin B (AMB). CAMB is a spiral-shaped phospholipid-cation precipitate that is primarily made up of phosphatidylserine — a naturally occurring phospholipid with a designation of generally recognized as safe (GRAS) from the FDA — and calcium. These multilayer cochleates are comprised of a solid lipid bilayer sheet, rolled into a spiral, with no internal aqueous space. This structure provides protection against degradation, which allows the inner structure to remain intact even after exposure to unfavorable environments (eg, low pH in the stomach), whilst providing the systemic delivery of AMB.

Historically, AMB has been considered the “gold standard” in antifungal treatments due to its broad spectrum of activity and lack of emergence of resistance. However, the use of AMB and its derivatives is limited by side effects, including nephrotoxicity, anemia and infusion related reactions. AMB disrupts the fungal cell wall via its high-affinity binding to ergosterol. The transmembrane channels that form as a result of this binding cause potassium to leak from the cell, thus initiating a lipid peroxidation cascade that causes irreversible damage to the cell.

CAMB demonstrates antifungal activity when administered orally. The efficacy is comparable to AMB but demonstrates reduced toxicity in animal models.

The sponsor changed the concentration of the study drug to a more concentrated formulation of 20mg/ml from the original concentration of 5mg/ml after participants in this study were on the extension phase. A 27.5 mg/mL concentration has been tested in a study of CAMB in Cryptococcal meningitis in 37 individuals and found to be well tolerated up to doses of 2.0grams daily. Due to viscosity concerns, however, the concentration was then changed to 20mg/ml. The dosing change has been submitted to the FDA and no concerns were reported.

After May 2020, the company will cease production of the 5mg/mL

concentration and move to the higher concentration of 20mg/mL.
The transition to the 20mg/ml concentrate will be implemented once the 5mg/ml study drug supply is dispensed and fully used by the subjects in the trial.

1.1.2 Summary of Previous Preclinical Studies

Oral delivery of AMB formulated as CAMB was evaluated by measuring the concentration of AMB in liver, kidney, and lung of *Candida albicans*-infected mice for 14 days.[1] Two groups of 10 mice were infected with *C. albicans* on Day 0. Beginning on Day 1, the mice were treated with either the oral CAMB formulation (10 mg/kg) or intraperitoneal (IP) deoxycholate solubilized AMB (DAMB [Fungizone®], 2 mg/kg). Mice from each group were euthanized at 4 hours postdose, and tissue and plasma samples were recovered on Days 1, 3, 5, 7, 11, and 15. The AMB levels in these samples were determined by reverse-phase high performance liquid chromatography. The tissue AMB levels for the orally dosed CAMB formulation ranged from 0.24 to 2.4 µg/g tissue throughout the treatment period. *In vitro* fungicidal activity measurements of AMB against *C. albicans* have indicated a minimum fungicidal concentration (MFC) at or below these levels. Thus, the AMB tissue levels observed in this study were clearly sufficient for antifungal efficacy. In contrast to the tissue levels, AMB plasma levels for the mice treated with the oral CAMB formulation were typically below 0.08 µg/mL. Despite relatively low plasma concentration, the orally administered CAMB appeared to be effectively transported to the tissues. It is possible that immune system phagocytes directly delivered CAMB to the sites of infection.

In another study of AMB protection against candidiasis infection in mice, infected animals were treated orally with AmBisome® (10 mg/kg) or CAMB (0.5, 2.5, 5.0, 10, or 20 mg/kg), or IP with DAMB (1.0 or 2.0 mg/kg).[2] Treatment with DAMB resulted in a 70% and 100% survival for the 1.0 and 2.0 mg/kg doses, respectively. Oral AmBisome at 10 mg/kg resulted in 90% survival. The CAMB-treated animals showed a 100% survival rate at all doses.

A mouse model was also used to compare the antifungal activities of CAMB and DAMB in treating mice with two levels of immunosuppression induced by cyclophosphamide therapy with *Aspergillus* infection. Oral administration of CAMB at 10 mg/kg per day for 10 days was protective against *Aspergillus*

infection, which was comparable to the protective effect of IP administered DAMB at 4 mg/kg per day (adjusted from average human dosage) after 10 days. Less immunosuppressed mice demonstrated a dose-dependent reduction in fungal tissue burden for all target organs. Fungal load in the liver and lung of mice orally treated with CAMB at 5 mg/kg/day was equivalent to the organ fungal load in mice IP treated with 4-mg/kg DAMB. However, treatment with CAMB at 20 mg/kg/day was required for maximum reduction of fungal load in the kidneys.

In the more immunosuppressed mice, oral administration of CAMB at 40 mg/kg/day resulted in a 90% survival rate in infected mice after 4 days, and a 70% survival rate on Day 14. This was compared to DAMB at 4 mg/kg/day, which offered only moderate protection. CAMB at 20 mg/kg/day produced a 70% survival rate after 4 days, and a 60% survival rate on Day 14. A 2-log to 3-log reduction in CFU/g of tissue was observed at CAMB doses ≥10 mg/kg/day, and *Aspergillus* was almost undetectable at doses above 20 mg/kg/day. Lower doses did prevent the spread of *Aspergillus* infection, but had less than 50% survival rates by Day 5.

This study also demonstrated that repeated oral administrations of CAMB are effective for tissue distribution, as was shown by the tissue-to-blood partition coefficient pattern that was similar to the organ distribution pattern, which indicates predictable penetration of the drug to target organ tissues. Nephrotoxicity was tested and shown to be significantly reduced in mice treated with CAMB compared to mice treated with DAMB.

A separate study using a rat and a dog model tested the toxicokinetic effect of oral administration of CAMB.[3] In this study, single daily doses were administered for 28 days. Dogs were dosed at 15, 30, or 45 mg/kg, and rats were dosed at 30, 45, or 90 mg/kg. In both models, CAMB was well tolerated at all doses with no mortalities or clinical abnormalities.

In dogs, AMB was detected at all 3 doses in the kidney, liver, and spleen, but was not detected in the lung. In rats, AMB was detected in the kidney and liver but not the spleen.

There were no major sex-related differences in plasma toxicokinetics of AMB. Accumulation of AMB was observed as a result of repeated single daily dosing, but no toxic effects were observed.

Overall, treatment with CAMB resulted in equal efficacy and reduced nephrotoxicity relative to treatment with DAMB.

1.1.3 Summary of Relevant Clinical Studies

In a Phase I study, using the drug concentration of 5mg/ml, subjects received a single dose of CAMB at 200 mg (approximately 3.3 mg/kg), 400 mg (approximately 6.7 mg/kg), or 800 mg (approximately 13.3 mg/kg). Pharmacokinetics (PK) was evaluated through 96 hours postdose, and safety was evaluated for 2 weeks after administration.

CAMB was well tolerated at 200 and 400 mg. Subjects recorded some mild gastrointestinal distress and nausea. There were no abnormalities in kidney function or other safety laboratories noted. The clinical observations were similar to what was observed in the animal toxicology studies.[4] Blood concentrations of CAMB peaked around 10 to 12 hours postdose and were undetectable by 48 hours postdose.

The 800-mg dose was not well tolerated, but there were no major adverse events (AEs). Increased nausea and gastrointestinal distress were observed, perhaps because the dose volume was high (160 mL). It appeared that 400 mg would be a proper upper limit for dosing, balancing efficacy, safety, and tolerability. Increasing the frequency of dosing might allow higher daily dosing. In order to improve the tolerability this study will use twice daily (BID) dosing. Though this study will include the potential to titrate up to a total daily dosage of 800 mg. The highest individual dose that will be used in this study will be 400 mg (80 mL).

The study drug was changed from a concentration of 5mg/ml to 27.5mg/mL for a study in Uganda addressing safety and efficacy in the treatment of Cryptococcal meningitis. Thirty-seven subjects were dosed with the 27.5mg/ml concentration, with a dose escalation up to 1.5g daily, with all participants tolerating the full dose, and no serious or unexpected adverse events. With a dose escalation up to 2.0g daily, 8 of 9 participants tolerated the study drug. One participant had grade 3 thrombocytopenia, that was not thought to be related to the study drug. Five of 9 participants had mild grade 1 GI side effects.

1.2 Rationale

As a result of the development of drug resistance, the current therapeutic options for mucocutaneous candidiasis are not as effective as they once were. Azole antifungals are available in oral formulations and typically well tolerated, but resistance can develop and toxicities occur, especially with prolonged use, including hepatotoxicity, fluoride toxicity, and photosensitivity (with voriconazole). Echinocandins (eg, caspofungin and micafungin) are very well tolerated but are only available as intravenous formulations and resistance can develop. AMB derivatives are used for their broad fungicidal activity, but they require parenteral administration and have significant side effects, such as nephrotoxicity, which worsens with longer courses of treatment. AMB administered as an oral solution is not widely available, is not very effective, and is irritating to the oral and esophageal tissues.

Our clinical group currently follows many patients with mucocutaneous candidiasis, some of whom have become refractory to standard or tolerated non-intravenous therapies. The majority of these patients have underlying immune deficiencies disrupting the Th17 lymphocyte/IL-17/IL-22 pathway, which leads to abnormalities in host control of mucocutaneous candidiasis. Examples include STAT3 deficient Hyper IgE syndrome, gain of function STAT1 defects, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), and IL-17/IL-22 autoantibodies from thymoma.

CAMB is a fungicidal, orally administered agent with a novel mechanism of absorption and distribution to infected tissues. Mouse studies have indicated that CAMB is well tolerated and is effective in eliminating *Candida* species infections and prolonging animal survival. Mouse and dog studies have also indicated lower toxicity for CAMB relative to its predecessor, intravenous DAMB. These animal studies also demonstrated the ability of CAMB to reach target organs efficiently, with quantifiable concentrations. A phase I trial in healthy volunteers reported no serious or dose-related AEs, with side effects being reported as mild nausea or mild gastrointestinal distress. Doses of 200 and 400 mg resulted in only mild AEs and no abnormal clinical or laboratory findings. A dose of 800 mg was also tolerated except for gastrointestinal (GI) symptoms which may have been related to the large volume (160 mL).

The ability to provide amphotericin B as an oral formulation as CAMB may offer a new and promising alternative for patients with mucocutaneous candidiasis refractory to tolerated available therapies.

2 Study Objectives

2.1 Primary Objective

The primary objective is to assess the clinical response to treatment of mucocutaneous candidiasis (OPC, EC, VVC) infections in patients who are refractory or intolerant to standard non-intravenous therapies after treatment for 14-days with the highest titrated dosage (Target Dosage) of CAMB per patient.

2.2 Secondary Objectives

- To assess the plasma, urine, and salivary PK of CAMB after a single dose and after multiple doses (14 days) for both the starting dosage and subsequent up-titrations.
- To assess the safety and tolerability of CAMB in OPC, EC, and VVC
- To assess mycological response in OPC, EC, and VVC
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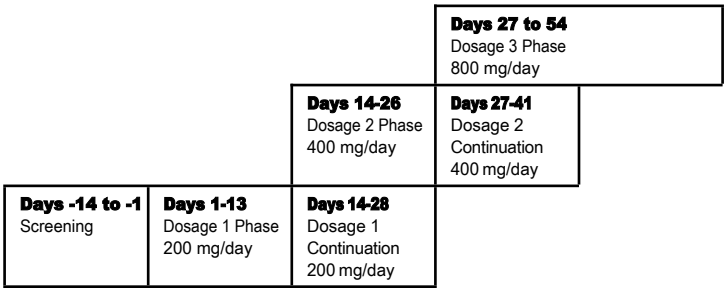
2.3 Exploratory Objective

- To assess the stool and vaginal secretion PK of CAMB after a single dose and after multiple doses (14 days) for both the starting dosage and subsequent up-titrations
- To assess clinical response in those patients with a concomitant diagnosis of OMC.
- To assess long-term (up to 60 months) safety and efficacy in those patients that qualify for extension (See Section 6.6).

3 Study Design

3.1 Description of the Study Design

This is an open-label, dose-titration study that will assess the efficacy, safety, tolerability, and PK of CAMB in patients with mucocutaneous candidiasis (OPC, EC, or VVC) who are refractory or intolerant to standard non-intravenous therapies. We plan to enroll 16 patients. Patients will be recruited largely from cohorts followed on NIAID protocols with the following underlying diseases: STAT3 deficient Hyper IgE syndrome, gain of function STAT1 mutations, APECED, and thymoma with auto-antibodies with IL-17/IL-22 pathway. These underlying diagnoses predispose patients to chronic mucocutaneous candidiasis through disruption of similar pathways, thus suggesting that the patients may have similar benefits to this study drug. However, if there are patients that do not have these underlying diseases but fit the inclusion and exclusion criteria, the patient may be enrolled at the investigator's discretion.



The study will include 14-day clinical evaluation periods. At the end of each dosing period, the investigator will make a determination to continue dosing the patient an additional 14 days with the same dosage or to escalate the dosage up to two times for an additional 14 days each time. The dosing phases are described below:

- 200 mg/day. On Day 1, patients will receive a single 100-mg dose of CAMB. Blood, urine, saliva, stool (optional), and vaginal secretions (optional) will be collected over the next 24 hours for PK analysis. Starting on Day 2, patients will receive 200 mg/day (100 mg BID) until Day 14. Study visits will be on Days 4 and 7. If on Day 14 the patient is determined to be a clinical responder and the drug is well tolerated, then they will receive a single 100-mg dose in the morning and blood, urine, saliva, stool (optional), and vaginal secretions (optional) will be collected over the next 24 hours for PK analysis. These patients will continue to receive 200 mg/day (100 mg BID) for the next 14 days. They will have a study visit on Days 21 and 28, and a final post treatment visit on Day 42.

- 400 mg/day. If on Day 14 the patient is determined to not be a clinical responder but the drug is well tolerated, then they will receive a single 200-mg dose in the morning. Blood, urine, saliva, stool (optional), and vaginal secretions (optional) will be collected over the next 24 hours for PK analysis. These patients will receive 400 mg/day (200 mg BID) for the next 14 days. They will have study visits on Days 17, 20, and 27. If on Day 27 they are determined to be a clinical responder and the drug is well tolerated, then they will receive a single 200-mg dose in the morning and blood, urine, saliva, stool (optional), and vaginal secretions (optional) will be collected over the next 24 hours for PK analysis. These patients will continue to receive 400 mg/day (200 mg BID) for the next 14 days. They will have a study visit on Days 34 and 41, and a final post treatment visit on Day 55.

- 800 mg/day. If on Day 27 the patient is determined to not be a clinical responder but the drug is well tolerated, then they will receive a single 400-mg dose in the morning. Blood, urine, saliva, stool (optional), and vaginal secretions (optional) will be collected over the next 24 hours for

PK analysis. These patients will receive 800 mg/day (400 mg BID) for the next 14 days. They will have study visits on Days 30, 33 and 40. If on Day 40 the patient is determined to not be a clinical responder, the study drug will be discontinued. At that point, follow-up procedures will be the same as an Early Termination Visit. If the patient is determined to be a clinical responder, the patient will continue to receive 800mg/day (400mg BID) for the next 14 days. They will have additional study visits on Days 47 and 54, and a final post treatment visit on Day 68.

- A long-term extension of up to 60 months of study treatment will be offered for patients who respond clinically to therapy and have no safety or tolerability concerns (See Section 6.6).

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint is the percentage of patients with a primary diagnosis of OPC, EC, or VVC who achieve Clinical Responder status after 14 days of treatment at the highest titrated CAMB dosage per patient (Target Dosage). Clinical Responder will be defined as patients who achieve Complete Clinical Cure or Clinical Improvement. The Clinical Response evaluation for each specific diagnosis of mucocutaneous candidiasis is described below:

OPC:

- Clinical Cure: Absence of plaques or ulcers and absent or minimal symptoms.
- Clinical Improvement: Partial resolution (≥ 50%) of pretreatment (Baseline) signs and symptoms.
- Clinical Failure: No improvement (< 50%) or worsening of pretreatment (Baseline) signs or symptoms.
- Not evaluable: Subject not evaluable due to lack of follow-up visits.

EC: Patients will undergo a research-indicated upper endoscopy to evaluate for esophageal candidiasis at the end of treatment or within 4 weeks of clinical improvement. Clinical cure will only be used for those patients who undergo this

endoscopy. If more than three patients decline to undergo this procedure, then this endpoint will be re-assessed.

- Clinical Cure: Absence of plaques or ulcers on endoscopy and absent or minimal symptoms.
- Clinical Improvement: Partial resolution (≥ 50%) of pretreatment (Baseline) symptoms or signs.
- Clinical Failure: No improvement (< 50%) or worsening of pretreatment (Baseline) signs or symptoms.
- Not evaluable: Subject not evaluable due to lack of follow-up visits.

VVC:

- Clinical Cure: Absence of signs and symptoms of vaginitis.
- Clinical Improvement: Reduction of ≥50% of the clinical severity score from Baseline.
- Clinical Failure: Worsening of symptoms or reduction in clinical score of <50% from Baseline.
- Not evaluable: Subject not evaluable due to lack of follow-up visits.

3.2.2 Secondary Endpoints

1. Plasma, urine, and salivary single-dose and steady-state PK parameters and disposition of oral CAMB.
2. Dose linearity/proportionality of oral CAMB with titration.
3. Clinical Responder status after 28 days at the Target Dosage.
4. Clinical Responder status after 14 days at each dosage level.
5. Mycological response after treatment for 14 days and 28 day with the Target Dosage.
6. Mycological response after treatment with each dosage level for 14 days.
7. Rate of treatment-limiting toxicity.
8. Rate of clinical relapse. Clinical relapse will be defined as a reoccurrence of clinical signs and symptoms after being sign and symptom free for 1 week.
9. Incidence of nephrotoxicity defined as an increase of more than 100% of

baseline serum creatinine.

10. Incidence of hypokalemia, defined as serum potassium ≤ 3 mmol/L during or within 3 weeks of completing treatment.
11. Incidence of AEs (see Section **11**)
12. Clinical Responder status after 14 days of treatment at the Target Dosage per patient of a secondary, less severe candida infection. Clinical Responder will be defined as patients who achieve Complete Clinical Cure or Clinical Improvement.

3.2.3 Exploratory Endpoints

1. Stool and vaginal secretion single-dose and steady-state PK parameters and disposition of oral CAMB.
2. To assess clinical response in those patients with a concomitant diagnosis of OMC.
3. Long-term (up to 60 months) safety and efficacy response.

4 Study Population

4.1 Rationale for Subject Selection

We will enroll patients with immunodeficiencies that result in recurrent or chronic mucocutaneous candidiasis, who are refractory or intolerant to standard non-intravenous therapies. The underlying diseases we expect these patients to have include, but are not limited to: STAT3 deficient Hyper IgE syndrome, gain of function STAT1 mutations, APECED, and thymoma with autoantibodies with IL-17/IL-22 pathway. If a patient has multiple *Candida* diagnoses, for example OPC and VVC or EC and VVC, the diagnosis that is more severe will be documented as the primary diagnosis and used in the primary endpoint analysis. However, all diagnoses will be evaluated and included in the secondary analysis.

Patients will be co-enrolled on 1 of the following NIAID protocols:

- 00-I-0159, Natural History, Management, and Genetics of the Hyperimmunoglobulin E Recurrent Infection Syndrome (HIES)
- 93-I-0119, Detection and Characterization of Host Defense Defects
- 07-I-0033, Screening Protocol for Detection and Characterization of

Infections and Infection Susceptibility

- 11-I-0187, The Natural History, Immunologic Correlates and Genetic Defects in Patients with Mucocutaneous and Invasive Fungal Infections
- 01-I-0202, Natural History, Genetics, Phenotype and Treatment of Mycobacterial Infections

We hope to enroll a minimum of 16 patients with OPC, EC, and/or VVC.

4.2 Patient Inclusion Criteria

- Age 18-75 years
- Patients must have a clinical diagnosis of at least one of the following:
  - Persistent OPC for greater than or equal to 5-days documented on at least one occasion by KOH or fungal stain and confirmed by mycological culture to be azole resistant within the previous 6 months and/or intolerance to standard non-intravenous therapies or lack of improvement or worsening of OPC after receipt of appropriately dosed oral azole therapy.
  - EC associated with clinical symptoms of retrosternal pain, odynophagia, and/or pain with swallowing and documented by esophageal biopsy or visualization with culture documenting azole resistance within the previous 6 months and/or intolerance to standard non-intravenous therapies or lack of improvement or worsening of EC after appropriately dosed azole therapy.
  - Persistent VVC for greater than or equal to 5-days as documented by presence of vaginal symptoms and a positive wet mount showing *Candida* structures and confirmed by a vaginal culture positive for *Candida* with azole resistance within the previous 6 months and/or intolerance to standard non-intravenous therapies or lack of improvement or worsening of VVC after receipt of appropriately dosed azole therapy.
- Patient is expected to survive for ≥ 6 months.
- Willing to have samples stored for future research.
- Agree to use highly effective contraception (see below).

Contraception: Because the effects of CAMB on the developing human fetus are unknown, sexually active patients of childbearing potential must agree to

use highly effective contraception as outlined below before study entry and for the duration of study participation. Females of childbearing potential must have a negative pregnancy test result before receiving CAMB. During the course of the study, if a patient becomes pregnant or suspects they are pregnant, then they should inform the study staff and their primary care physician immediately. Acceptable forms of contraception are:

- Intrauterine device (IUD) or equivalent.
- Hormonal contraceptives (eg, consistent, timely and continuous use of contraceptive pill, patch, ring, implant, or injection that has reached full efficacy prior to dosing). If the patient uses contraceptive pill, patch, or ring, then a barrier method (eg, male/female condom, cap, or diaphragm plus spermicide) must also be used at the time of potentially reproductive sexual activity.
- Be in a stable, long-term monogamous relationship, per PI assessment, with a partner that does not pose any potential pregnancy risk, eg, has undergone a vasectomy at least 6 months prior to first dose of study agent or is of the same sex as the patient.
- Have had a hysterectomy and/or a bilateral tubal ligation or both ovaries removed

4.3 Patient Exclusion Criteria

- Allergy to any AMB product or any component of CAMB (eg, phosphatidylserine)
- Have evidence of systemic fungal infections requiring intravenous antifungal therapy
- Pregnant or nursing women, and women intending to become pregnant during the study period
- Had a concomitant medical condition that could interfere with study drug evaluation or that is a contraindication to the proposed investigational treatment based upon known agent safety profile or toxicities.
- Had any of the following laboratory abnormalities at the screening visit:
    - Alanine Transaminase (ALT), Aspartate Transaminase (AST) and Alkaline phosphatase (ALP) >2.5 times the upper limit of normal (ULN).

- Total bilirubin level > 2.5 times the ULN
- Serum creatinine level > 2 times the ULN
- Absolute neutrophil count less than 500 cells/μL
- Potassium level <3.5 mmol/L

- Exposure to any investigational agent within 4 weeks prior to Day 0 (Baseline).
- Current or recent history (past 12 months) of drug or alcohol abuse.
- Use of intravenous AMB products within 1-week of start of study drug administration
- Use of non-intravenous AMB products (such as oral AMB swishes) within 72 hours prior to start of study drug administration
- Any other condition the investigator believes would interfere with the patient's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk.

Co-enrollment Guidelines:

Co-enrollment in other trials is restricted, other than enrollment on observational studies. Consideration for co-enrollment in trials evaluating the use of a licensed medication will require the approval of Principal Investigator and Sponsor. Study staff should be notified of co-enrollment as it may require the approval of primary investigator.

4.4 Justification for Exclusion of Special Populations

Exclusion of Women

- **Pregnancy:** Pregnant women are excluded from this study because the effects of CAMB on the developing human fetus are unknown, and there is the potential for teratogenic or abortifacient effects.

- **Breastfeeding:** Patients who are breastfeeding should cease when being treated with CAMB because of the potential risk for AEs in nursing infants.

Exclusion of Children

Children are not eligible for this study because this is an investigational study with very limited experience in humans regarding safety and appropriate dosing.

We hope that the results of this study will then allow further study including in pediatric patients.

Exclusion of Adults Lacking Capacity to Provide Consent

If participants permanently lose the ability to provide ongoing consent subsequent to giving initial consent, they will be withdrawn from the study (section 11.9).

5 Study Agent/Interventions

5.1 Disposition and Dispensation

Study agent will be distributed via the NIH Pharmacy according to standard pharmacy procedures.

5.1.1 Study Drug Packaging and Labeling

The CAMB will be packaged into Nalgene™ amber PETG 125-mL square bottles with HDPE closures. The corresponding labels are:

Protocol: MB-70004
Subject ID: _____
Investigator Phone Number:
_____
Encochleated Amphotericin B Suspension (CAMB)
For Oral Use
5 mg/mL Amphotericin B
Lot#: XXXXXXXX*
Contents: XXX mL
Take as directed by Study Investigator
Shake well before use.
Store refrigerated at 2-8° C. Protect from the light.
Caution: New Drug – Limited by Federal Law to Investigational Use.
Matinas BioPharma Nanotechnologies, Inc. Bedminster, NJ

*Actual values will be listed on Study Drug label.

Patients will be supplied with measuring tools (eg, dispensing cups or syringes) to take home and use for study drug administration and will be instructed on how

to use them.

5.2 Study Agent Storage and Stability

5.2.1 Study Drug Storage

All study drug will be stored in a locked area. The area will be free of environmental extremes and with a limited access. Study drug will be kept refrigerated at 2°C to 8°C. The site will maintain records of storage temperature and make them available for Sponsor review.

Patients will be instructed to store study drug in a refrigerator at 2°C to 8°C (36°F-46°F). In order to travel with study drug, patients will be provided a cooler bag and freezer pack to maintain temperature.

5.3 Description, Preparation, and Administration of Study Drug Product

5.3.1 Description

CAMB is a yellow-to-orange suspension that is homogenous upon shaking. It should be stored between 2°C and 8°C. CAMB is light-sensitive and should be stored away from light.[5] However, exposure of < 4 hours to fluorescent light and excursions of up to 24 hours at room temperature are acceptable. In this study, CAMB was initially provided at a concentration of 5 mg/mL and administered at up to 3 strengths: 100, 200, and 400 mg.
After May 31, 2020, the company has ceased production of the 5mg/mL concentration and move to the higher concentrated formulation of 20mg/mL.

Preparation, Dosing and Administration

The study drug will be provided as an oral suspension. Patients will take the study drug twice per day to reach the total daily dose. Prior to administration, the study drug container will be shaken, the required quantity poured into a dispensing cup, and the remainder of the study drug returned to refrigerated storage. Patients with OPC and/or EC will be asked to swish the suspension in their mouths before swallowing and then refrain from eating or drinking for 30 minutes post-dose. Patients with VVC and/or OMC will be asked to drink suspension without swishing. CAMB is provided at a single concentration

(20 mg/mL). Patients will be instructed to dispense the appropriate volume of solution ($5, 10 \text{ or } 20 \text{ mL}$) to reach the target dose, according to the following table:

Total Daily Dose (mg/day)	Single Dose (mg/dose)	Single Dose Volume, 5mg/mL concentration (mL)	Single Dose Volume, 20mg/mL concentrations (mL)
200	100	20	5
400	200	40	10
800	400	80	20

5.3.2 Dose Adjustments/Modifications/Delays

If the GFR falls below 60 mL/min/1.73m^2 or 30% lower than baseline then we will suspend treatment until GFR returns to baseline, in consultation with the safety monitoring committee.

For other toxicities thought to be the result of the study drug, including gastrointestinal symptoms, treatment will be suspended until the symptoms resolve. The investigator and patient will consider re-initiation on the basis of clinical findings and symptom severity.

5.3.3 Duration of Therapy

Subjects will take the study drug for 28 days at the clinically effective tolerated dosage (Target Dosage). However, if study drug is tolerated and the patient has clinical efficacy at two weeks, the extension phase of the protocol will be offered, in which the patient can continue the study drug for up to 60 months.

5.3.4 Tracking of Dose

Study drug bottles will be returned to assess adherence. Patient medication logs will also be used to aid with adherence.

5.3.5 Limitations on Prior Therapy

Subjects may continue other pre-existing chronic (> 2 weeks) antimicrobial therapies including azole antifungals. Intravenous amphotericin products will be

stopped at least 1 week before initiation of the study drug, and non-intravenous amphotericin products (such as oral AMB swishes) will be stopped at least 72 hours before initiation of the study. Other antimicrobial agents that are added during the course of the study need to be approved by one of the investigators.

5.4 Study Product Accountability Procedures

The dispensing pharmacy will acknowledge receipt of all shipments of investigational drug product and maintain accurate accountability records. The study drug administered to the subject will be documented in the medical record. All study drug will be stored and disposed of according to the manufacturer's recommendations. At each monitoring visit and the conclusion of the study, an inventory of study drug will be performed by the Study Monitor (or designee) and the Investigator (or designee). Any missing supplies must be indicated on the drug accountability form along with an explanation of the discrepancy. The Investigator will be instructed to return all unused study drug to Aquarius or designee, and return a copy of the Clinical Supplies Return Form.

5.5 Concomitant Medications and Procedures

Medications to be reported in Clinical Research Information Management System of the NIAID (CRIMSON) are concomitant prescription medications, over-the-counter medications, and non-prescription medications taken at the time of AEs (all grades).

5.6 Drug Interactions

CAMB should be used with caution in patients receiving chemotherapy with certain agents, in patients receiving lymphocyte transfusions, or curare-class paralytic agents. Concurrent use of CAMB with drugs that lower serum potassium requires monitoring of serum potassium levels. Other drugs that have increased risk in the presence of hypokalemia should be used with caution, including digitalis and neuromuscular blockade agents (paralytics). The following drugs are known to interact with AMB and may interact with CAMB:

Antineoplastic Agents

Concurrent use of antineoplastic agents may enhance the potential for renal toxicity, bronchospasm, and hypotension. Antineoplastic agents should be given

concomitantly with caution.

Corticosteroids and Corticotropin

Concurrent use of corticosteroids and corticotropin may potentiate hypokalemia, which could predispose the patient to cardiac dysfunction. If used concomitantly with CAMB, then serum electrolytes and cardiac function should be closely monitored.

Digitalis Glycosides

Concurrent use may induce hypokalemia and may potentiate digitalis toxicity. When administered concomitantly, serum potassium levels should be closely monitored.

Flucytosine

Concurrent use of flucytosine may increase the toxicity of flucytosine by possibly increasing its cellular uptake and/or impairing its renal excretion.

Azoles

In vitro and in vivo animal studies of the combination of AMB and imidazoles suggest that imidazoles may induce fungal resistance to AMB. Combination therapy should be administered with caution, especially in immunocompromised patients.

Leukocyte Transfusions

Acute pulmonary toxicity has been reported in patients simultaneously receiving intravenous AMB and leukocyte transfusions.

Other Nephrotoxic Medications

Concurrent use of AMB and other nephrotoxic medications may enhance the potential for drug-induced renal toxicity. Intensive monitoring of renal function is recommended in patients requiring any combination of nephrotoxic medications.

AMB-induced hypokalemia may enhance the curariform effect of skeletal muscle relaxants (eg, tubocurarine) due to hypokalemia. When administered concomitantly, serum potassium levels should be closely monitored.

5.7 Prohibited Medications and Procedures

Concomitant treatment with all AMB products including liposomal formulations and oral AMB will not be permitted.

Azole antifungals will be permitted if used for another indication besides treatment of Candida infection, such as for the treatment or prevention of mold infection.

6 Study Schedule

See Appendix B for tabulated schedule of procedures and evaluations. See Appendix C for volumes of blood to be collected at each visit. Study visits will take place at the NIH Clinical Center, with the exception of certain sample collections that may be done at a local laboratory as indicated below. Patients may be admitted to the Clinical Center as inpatients on the days that 24-hour PK samples are collected.

6.1 Screening

Enrolled patients will be followed on one of the NIAID protocols that allows treatment and evaluation of underlying immune defects, including protocols #00-I-0159, 93-I-0119, 07-I-0033, 11-I-0187, and 01-I-0202. The eligibility criteria, including medical history and physical examination findings, will be evaluated from the immunologic, genetic, and/or initial infection work up conducted as part of the referring protocol. Laboratory, history, and exam findings to fulfill inclusion and exclusion criteria must be collected within 2 weeks prior to enrollment in this protocol (See Appendix B Schedule of Procedures/Evaluations). If findings are not available from the referring protocol within that timeframe, then physical exam, medical history, blood and urine collection, pregnancy test, and microbiology will be conducted under this protocol. Patients with signs and symptoms of esophageal candidiasis will have an upper endoscopy performed under this protocol within 4 weeks before study drug initiation to document the extent of disease and to allow for biopsy and/or visualizing with culture swabs. Patients will sign an informed consent document before undergoing any research procedures under this protocol.

6.2 Baseline

On Study Day 0, patients will undergo the following procedures:

- Medical/Medication history
- Baseline clinical assessment of *Candida* infection

- Physical exam
- Blood draw and urine collection (see section 7.4) if screening was more than 72 hours prior
- Microbiology (fungal culture of affected site of *Candida* infection, see section 7.3), with the exception of esophageal cultures
- Optional collection of peripheral blood mononuclear cells (PBMCs) for storage
- Optional vaginal secretions collection

If the screening evaluations were conducted with 72 hours of the baseline visit, then blood draw, urine, and vaginal swab collection will not be repeated at baseline.

6.3 Treatment at 200 mg/day

On Study Day 1, patients will undergo clinical assessment and physical exam, and assessment of AEs and concomitant medications. Blood and urine will also be collected for additional laboratory evaluations (see Section 7.4). Patients who are capable of becoming pregnant will have a pregnancy test. Predose blood and saliva PK samples will be collected. Patients will then receive a single 100-mg dose of CAMB, followed by 24-hour PK sampling of blood., urine, saliva, stool (optional), and vaginal secretions (optional).

On Study Day 2, the 24-hour timepoint samples of blood , urine, saliva, stool (optional), and vaginal secretions (optional) will be collected. Patients will undergo assessment of AEs and concomitant medications. Blood will also be collected for additional laboratory evaluations. Patients will then begin 100-mg BID dosing for 14 days. Urinalysis for laboratory evaluation will be collected after the 24-hour urine PK concludes and can be collected after administering the morning dose of study drug.

On Study Day 4 (± 1 day), the following procedures and evaluations will be performed:

- Clinical assessment and physical exam as needed to evaluate new symptoms/complaints
- Assessment of AEs and concomitant medications
- Blood draw and urine collection

On Study Day 7 (± 1 day), the following procedures/evaluations will be performed:

- Assessment of AEs and concomitant medications
- Blood draw and urine collection

For this time point, the patient and the investigator have the option of doing a phone interview and obtaining the blood and urine lab work at a local laboratory. A copy of the results should be sent to the investigator.

On Study Day 14 (± 3 days), before administration of the morning dose, patients will undergo clinical assessment and physical exam with clinical response calculation, and assessment of AEs and concomitant medications. Patients who are capable of becoming pregnant will have a pregnancy test. If the patient is a Clinical Responder and the drug is well tolerated, then the dosage of 100 mg BID will be extended for 14 more days. The patient will only receive the morning dose on Day 14 and the following procedures/evaluations will be performed:

- Blood draw and urine collection
- Collection of 24-hour PK samples: Predose (0-hour timepoint) blood and saliva will be collected, followed by 24-hour PK sampling of blood., urine, saliva, stool (optional), and vaginal secretions (optional)
- Plasma , urine, stool (optional), salivary, and vaginal secretions (optional) 24-hour timepoint to be collected on Day 15.
- Microbiology (fungal culture of affected site)
- Optional collection of PBMCs for storage

On Study Day 21 (± 3 days), the following procedures/evaluations will be performed:

- Assessment of AEs and concomitant medications
- Blood draw and urine collection

For this time point, the patient and the investigator have the option of doing a phone interview and obtaining the blood and urine lab work at a local laboratory. A copy of the results should be sent to the investigator.

On Study Day 28 (± 3 days), the following procedures/evaluations will be performed:

- Clinical assessment and physical exam

- Endoscopy with biopsies for EC patients (within 4 weeks of clinical improvement)
- Assessment of AEs and concomitant medications
- Blood draw and urine collection
- Pregnancy testing
- Trough plasma PK collection
- Microbiology (fungal culture of affected sites)
- Optional collection of PBMCs for storage

Study Day 42 (± 3 days) will be the post-treatment End of Study visit for patients who continued 200 mg/day. For this visit, the patient and the investigator have the option of doing the assessment over the telephone instead of making a clinical visit. In this instance the laboratory testing should be performed by a local laboratory and a copy of the results should be sent to the investigator. The following procedures/evaluations will be performed:

- Assessment of AEs
- Blood draw and urine collection

6.4 Dose Escalation to 400 mg/day

If on Day 14 the patient is determined to not be a Clinical Responder but the study drug is well tolerated, then the dosage will be increased to 400 mg/day. These patients will receive only the morning dose (200 mg) on Day 14. The following procedures will be performed:

- Blood draw and urine collection
- Pregnancy testing (result confirmed before administration of dose)
- Collection of 24-hour PK samples: Predose (0-hour timepoint) blood and saliva will be collected, followed by 24-hour PK sampling of blood., urine, saliva, stool (optional), and vaginal secretions (optional)
- Plasma , urine, stool (optional), salivary, and vaginal secretions (optional) 24-hour timepoint to be collected on Day 15
- Microbiology (fungal culture of affected site)
- Optional collection of PBMCs for storage

Starting on Day 15, patients will be dosed with 400 mg/day (200 mg BID) for 14 days. Prior to dosing, patients will undergo assessment of AEs and concomitant medications. Blood will also be collected for additional laboratory evaluations. Patients will then begin 200-mg BID dosing for 14 days. Urinalysis for laboratory evaluation will be collected after the 24-hour urine PK concludes

and can be collected after administering the morning dose of study drug. Study visits will be on Days 17 (± 2 days), 20 (± 2 days), 27 (± 3 days), 34 (± 3 days), and 41 (± 3 days). Clinical assessment and physical exam, assessment of AEs and concomitant medications, blood draw, and urine collected will be conducted on Days 17, 27 and 41. As with the Day 7 visit, the evaluations for Day 20 can be conducted locally, with blood and urine collected from the patient's local diagnostic laboratory.

On Day 27 before administration of the morning dose, patients will undergo clinical assessment and physical exam with clinical response calculation, and assessment of AEs and concomitant medications. Patients who are capable of becoming pregnant will have a pregnancy test. If the patient is a Clinical Responder and the drug is well tolerated, then the dosage of 200 mg BID will be extended for 14 more days. The patient will only receive the morning dose on Day 27. Patients will undergo blood draw for research testing and optional collection of PBMCs for storage, urine and fungal culture of the affected site. Samples of blood , urine, saliva, stool (optional), and vaginal secretions (optional) for 24-hour PK analysis will also be conducted, the same as at Day 14.

As with the Days 7 and 20 visits, the visit for Day 34 can be conducted locally, with blood and urine collected from the patient's local diagnostic laboratory.

On Study Day 41 (± 3 days) the following procedures/evaluations will be performed:

- Clinical assessment and physical exam
- Endoscopy with biopsies for EC patients (within 4 weeks of clinical improvement)
- Assessment of AEs and concomitant medications
- Blood draw and urine collection
- Pregnancy testing
- Trough plasma PK collection
- Microbiology (fungal culture of affected sites)
- Optional collection of PBMCs for storage

Study Day 55 (± 3 days) will be the post-treatment End of Study visit for patients who continued 400 mg/day. For this visit, the patient and the investigator have the option of having a phone assessment instead of making a clinical visit. In this

instance the laboratory testing should be performed by a local laboratory and a copy of the results should be sent to the investigator. The following procedures/evaluations will be performed:

- Assessment of AEs
- Blood draw and urine collection

6.5 Dose Escalation to 800 mg/day

If on Day 27 the patient is determined to not be a Clinical Responder but the study drug is well tolerated, then the dosage will be increased to 800 mg/day. These patients will receive only the morning dose (400 mg) on Day 27. The following procedures will be performed:

- Blood draw and urine collection
- Pregnancy testing (result confirmed before administration of dose)
- Collection of 24-hour PK samples: Predose (0-hour timepoint) blood and saliva will be collected, followed by 24-hour PK sampling of blood, urine, saliva, stool (optional), and vaginal secretions (optional)
- Plasma, urine, stool (optional), salivary, and vaginal secretions (optional) 24-hour timepoint to be collected on Day 28
  Microbiology (fungal culture of affected site)
- Optional collection of PBMCs for storage

Starting on Day 28, patients will be dosed with 800 mg/day (400 mg BID) for 14 days. Prior to dosing, patients will undergo assessment of AEs and concomitant medications. Blood will also be collected for additional laboratory evaluations. Patients will then begin 400-mg BID dosing for 14 days. Urinalysis for laboratory evaluation will be collected after the 24-hour urine PK concludes and can be collected after administering the morning dose of study drug. Study visits will be on Days 30 (± 2 days), 33 (± 2 days), 40 (± 3 days), 47 (± 3 days), 54 (± 3 days) and 68 ((± 3 days). Clinical assessment and physical exam, assessment of AEs and concomitant medications, blood draw, and urine collected will be conducted on Days 30, 40, and 54. As with the Day 7 visit, the evaluations for Days 33 and 47 can be conducted locally, and blood and urine can be collected from the patient's local diagnostic laboratory.

At the Day 40 Study Visit, patients will be assessed for clinical response to study drug. If the patient is determined to not be a clinical responder, the study drug

will be discontinued. Follow-up will occur two weeks later (Day 54 +/- 3 days) and include all of the procedures performed at an Early Termination visit.

If the patient is a clinical responder, (s)he will only receive the morning dose on Day 40. Procedures will be the same as on Day 27.

On Study Day 54 (± 3 days), the following procedures/evaluations will be performed:

- Clinical assessment and physical exam
- Endoscopy with biopsies for EC patients (within 4 weeks of clinical improvement)
- Assessment of AEs and concomitant medications
- Blood draw and urine collection
- Pregnancy testing
- Trough plasma PK collection
- Microbiology (fungal culture of affected sites)
- Optional collection of PBMCs for storage

Study Day 68 (± 3 days) will be the post-treatment End of Study visit for patients who continued 800 mg/day. For this visit, the patient and the investigator have the option of doing the visit locally instead of making a clinical visit. In this instance the laboratory testing should be performed by a local laboratory and a copy of the results should be sent to the investigator. The following procedures/evaluations will be performed:

- Assessment of AEs
- Blood draw and urine collection

6.6 Extension of Study Drug

Many of the patients expected to enroll into this study have underlying immunodeficiencies that predispose them to chronic mucocutaneous candidiasis, and recurrence is highly likely when the study drug is stopped. Therefore, study participants who are tolerating the study medication and are clinical responders, will be permitted to enroll in a study extension. The extension may be continued from the end of the period of medication administration (i.e. the end of the 2 week period of study medication at the dose that allows efficacy and tolerance of drug) or the participant may have a break of study medication before re-starting the extension period. If there is a break between the initial study drug use and the extension phase, the subjects will be offered alternative antifungals, such as

topical amphotericin swish and spit, to help control the oral pharyngeal candida infection. Breaks in study drug extension will be minimized as much as possible. Any break through infections may be treated by either the Principle Investigator or the subject's Primary Care Provider. In case of recurrence or worsening of the mucocutaneous candida infections while on the extension part of the study drug, despite excellent adherence, that requires new or additional antifungals, the Principal Investigator will stop the study drug.

Study drug will be continued at the minimum dose (100mg BID, 200mg BID, or 400mg BID) meeting clinical responder criteria with good tolerance. The investigator will have the ability to change daily dosage and frequency of study drug based on patient response and tolerability between the range of 200 mg to 800 mg per day.

Extension of study medication will be offered if the following criteria are met:

- Clinical responder status for oral, esophageal or vaginal disease at the end of the 2 week study point at the highest tolerated dose to which they respond (Day 14 for 200 mg, Day 27 for 400 mg, or Day 40 for 800 mg).
- The study participant does not have any of the laboratory criteria meeting the exclusion criteria
    - Alanine Transaminase (ALT), Aspartate Transaminase (AST) and Alkaline phosphatase (ALP) >2.5 times the upper limit of normal (ULN).
    - Total bilirubin level > 2.5 times the ULN
    - Serum creatinine level > 2 times the ULN
    - Absolute neutrophil count less than 500 cells/μL
    - Potassium level <3.5 mmol/L
- Good tolerance of study drug
    - No gastrointestinal toxicity (nausea/vomiting/diarrhea) that is interfering with the ability to perform regular every day activities.
    - Less than two Grade 3 events and/or one Grade 4 event that are possibly, probably, or definitely related to participation in the trial;
    - No SAEs that are possibly, probably or definitely related to the study drug.
- No laboratory abnormalities, intercurrent illness, other medical condition or situation that occurs such that continued participation in the study would not be in the best interest of the subject.

Study medication will be allowed to continue for up to 60 months with the following monitoring:

- Bi-weekly safety laboratories (or more frequently as per PI discretion) including CBC/diff, chemistry panels (hepatic, mineral and acute). These can be performed at the NIH clinical center or at the home laboratory. (+/- 4 days)
- Bi-weekly visits to the NIH clinical center (+/- 3 days) for the first 1 month and then the visits can be extended to every 12 weeks (+/- 7 days) unless clinically indicated to be more frequent. At these visits the following study procedures will be performed:
    - Clinical assessment and physical exam
    - Assessment of AEs and concomitant medications
    - Blood draw including CBC/diff, chemistry panels (hepatic, mineral and acute), and urinalysis.
    - Pregnancy testing (except week 2 NIH visit after start of extension phase)
    - Serum and PBMCs may be collected for storage
    - Urine, plasma, stool, saliva and vaginal secretions may be collected and stored
    - Microbiology (fungal culture of affected sites)
    - OMC Picture of affected areas every 8 weeks

If study participants are only seen every 12 weeks, they will be contacted by phone or NIH-approved video conference platform at the 2-week interim point to assess for AEs, concomitant medications, and drug compliance. The laboratory testing can be performed by a local laboratory and a copy of the results should be sent to the investigator.

6.7 Early Termination Visit

All effort will be made to conduct an early termination visit for subjects who withdraw from the study. This visit will include all of the procedures performed at the normal end-of-study visit, with the exception of collection of plasma , urine, saliva, stool (optional), and vaginal secretion (optional) samples for PK analysis.

7 Study Procedures/Evaluations

7.1 Clinical Evaluations

At each study visit that requires a clinical assessment per protocol, the investigator will examine the patient and document the clinical signs and symptoms according to the scales described below.

Clinical Response Oropharyngeal/Esophageal Candidiasis:

The investigator will examine the oral cavity and question the subject to identify any signs/symptoms of infection and categorize clinical response to treatment.

The presence of plaques will graded according to the following scale, modified from an AIDS Clinical Trial Group (ACTG) Protocol:

- 0 None = Absent
- 1 Minimal = 1-5 discrete plaques and/or one confluent plaque ≤ 3 cm in longest length
- 2 Diffuse = Plaques that are more than minimal extent; or presence of ulcers
- 3 Worse = Plaques were clearly worse than on previous visit

The severity symptoms (dysphagia, odynophagia, retrosternal pain, oral pain, burning of mouth) will be graded according to the following scale:

- 0 None = Symptom was not present.
- 1 Mild = Symptom was present, but no or minimal interference was noted with eating.
- 2 Moderate = Symptom(s) present and led to interference with eating many foods.
- 3 Severe = Symptom(s) were very marked. The subject was unable to eat most foods.

The sum of the symptom scores will be used as the severity score.

Clinical Response Vulvovaginal Candidiasis:

The investigator will examine the patient and question the subject to identify any signs/symptoms of infection and categorize clinical response to treatment. The following signs and symptoms will be evaluated in each patient:

- Vaginal erythema
- Vulvovaginal pruritus
- Vaginal discharge

The severity of each symptom will be graded according to the following scale:

- 0 = Absent
- 1 = Mild
- 2 = Moderate
- 3 = Severe

The sum of the scores for all symptoms will be used as the severity score.

Clinical Response OMC:

The investigator will assess the signs and symptoms of OMC. For clinical response, the target thumbnail or great toenail will be assessed for the presence, absence, or improvement of OMC and subungual hyperkeratosis, and percentage of nail involvement will be estimated. Pictures will be taken every 2-weeks to document changes. The pictures will be taken by a medical photographer and will not contain identifiable information. Patients will sign the standard NIH photography consent form before pictures are taken, and may decline photography.

7.2 Endoscopic Evaluations

Patients with a diagnosis of EC will undergo a clinically indicated endoscopic evaluation under either conscious sedation or general anesthesia within 4 weeks before study drug initiation. These patients will also undergo a second endoscopy for research purposes only at end of treatment or within 4 weeks of clinical improvement, whichever occurs first. Each endoscopic evaluation will be graded according to the following scale:

- 0 None = Absent

- 1 Minimal = 1 to 5 discrete plaques and/or one confluent plaque ≤ 3 cm in longest length
- 2 Diffuse = Plaques that are more than minimal extent; or presence of ulcers
- 3 Worse = Plaques were clearly worse than on previous visit

7.3 Mycological Evaluations

All patients will undergo mycological evaluations at baseline and specified follow-up visits. Samples will be collected by swabbing the affected site. Portions of tissue leftover from clinically indicated biopsies may also be requested for mycological analysis. Results of mycological evaluations will be presented semi-quantitatively as:

- No growth
- One colony
- Scant
- Light
- Moderate
- Heavy
- Indeterminant: Extenuating circumstances preclude classification.

Measures of mycological response will include:

- Eradication: No growth.
- Partial response: Decrease in quantity of *Candida* from pre-treatment levels (eg, from heavy to scant).
- Persistence: No change or a worsening in *Candida* burden from pre-treatment levels.
- Relapse: A patient has achieved eradication or partial response initially, only to have the infection develop again after initial response or eradication.

7.4 Laboratory Evaluations

Stool, Saliva, and Vaginal Secretions

Stool, saliva, and vaginal secretions will be collected for PK analysis and may be used for other immunologic or microbiologic studies. Collection of stool and vaginal secretions is optional. Stool samples will be continuously collected (as available) for 24-hour PK analysis at the NIH Clinical Center on specified days. Saliva samples will be collected at pre-dose, 8 (± 3 hours) and 24 hours (± 1 hour) postdose for 24-hour PK analysis. Vaginal fluid will be collected by the

patient using the Instead™ Softcup (Evofem, Inc [San Diego, CA, USA]), a menstrual fluid collection device. The patient will insert the Softcup 24 hours postdose. After 2 hours, the patient will remove the cup and place it in a urine specimen container. There is a risk of dislodging an IUD with the Softcup; therefore, vaginal fluid collection will not be done in patients with IUDs. Vaginal fluid collection will be deferred during a patient's menstrual period and will not be done in patients who have had a hysterectomy with cervix removal.

In the study drug extension phase vaginal fluid will be collected by the subject using the Instead™ Softcup. The subject will insert the Softcup and remove it after 60 seconds and place it in a Falcon tube container. Vaginal collection is done unrelated to study drug administration time.

Urine

Urinalysis includes appearance, glucose, bilirubin, ketone, specific gravity, pH, protein, urobilinogen, nitrite, leukocyte esterase, white blood cell count, red blood cell count, hemoglobin.

Urine will also be continuously collected for 24-hour PK analysis on specified days.

Serum/Urine Pregnancy Test

A serum or urine pregnancy test will be given to women of childbearing potential as noted in the Study Schedule. Pregnancy prevention reminders and assessment of compliance will be done at each visit for subjects capable of becoming pregnant.

Blood Draws

Research evaluations on blood may include, but are not limited to, the following laboratory tests:

- PK
- Hematology: complete blood count with differential and platelet count
- Acute care panel, mineral panel, and hepatic panel

Plasma and PBMCs may be collected for storage. Plasma for 24-hour PK analysis (6 mL) will be collected in purple top K2-EDTA tubes at predose and 1 (± 5 minutes), 2 (± 5 minutes), 4 (± 15 minutes), 8 (± 15 minutes),

10 (± 15 minutes), 12 (± 15 minutes), and 24 hours (± 1 hour) postdose on specified days. Intravenous lines will be placed to facilitate multiple sample collections over 24 hours. Samples will be processed to measure plasma concentrations via a validated liquid chromatography with tandem mass spectrometry assay (LC-MS/MS).

8 Potential Risks and Benefits

8.1 Potential Risks

CAMB: There is limited experience in humans for the study drug. In the only clinical study on CAMB, side effects included nausea, abdominal pain, vomiting, and diarrhea. There was one instance of a moderate upper respiratory tract infection in a participant dosed with 800 mg of CAMB, but this was determined to not be related to CAMB. Risks associated with non-enchochleated formulations of AMB include nephrotoxicity, change in clotting factors, anemia, gastrointestinal intolerance, allergic reaction, or other unknown risks to this medication. These effects have not been observed in healthy humans dosed with CAMB.[5] There is also the possibility that this treatment will have no effect on the fungal infection for which it is being used so the infection may worsen. It is possible that the Candida infecting or colonizing the study participant could become resistant to amphotericin due to the exposure to the study drug. This could limit treatment response to systemic intravenous amphotericin potentially in the future.

The effects of CAMB on the developing fetus are unknown. Therefore, patients must use appropriate and effective forms of contraception to avoid becoming pregnant or to avoid impregnating their partner.

Endoscopy and Biopsies: Diagnostic endoscopy when performed by a trained endoscopist is generally safe and well tolerated. Cardiopulmonary complications may account for over 50% of the reported complications, with the majority the result of aspiration, over-sedation, hypoventilation, vasovagal episodes, and airway obstruction.[6-9] Significant complications can occur as a result of instrumentation, such as bleeding, perforation, and infection, with an overall frequency that approximates 0.1% for upper endoscopy.[10,11] The risk of perforation and/or death is approximately 0.001%, but varies with the condition of the patient and performance of special procedures such as biopsy.[12] These endoscopic complications were determined from elderly hospitalized patients, so the exact risk is unknown in the population for the current study.

NIH gastroenterologists have extensive experience with performing multiple endoscopic biopsies for research purposes and have found these well tolerated without appreciably increasing the risk of otherwise routine endoscopy.[13] In this work, they performed a retrospective review of 253 research endoscopies, for which an average of 38 biopsies was obtained per patient. No major complications were identified. Minor complications occurred and included self-limited bleeding and or pain in 5% of subjects. There was no statistically significant association between the number of biopsies, type of procedure, location of research biopsies and the risk of complications.

As a general practice, the risk of the procedure is minimized by monitoring pulse, blood pressure, and oxygen saturation throughout the procedure and by providing inpatient monitoring after the procedure.

In order to prevent complications and minimize their impact, we will avoid over-insufflation during biopsies, and provide post-procedure instructions for patients to recognize early warning signs of significant complications (eg, abdominal pain, fever, hematemesis, melena, chest pain and increased dysphagia) while providing mechanisms for early evaluation and treatment at the NIH CC (providing patient with contact information for on-call physician, study

team being available to address concerns, having emergency radiology, surgical consultation, and endoscopy available).

Conscious Sedation: Conscious sedation may be used in some patients undergoing endoscopy. Sedative drugs will be provided by CCMD and/or experienced anesthesiologists of the NIH CC. Side effects from sedative medications include cardiovascular and respiratory depression manifested by bradycardia, hypotension, respiratory acidosis, and apnea. Additional adverse reactions reported with these drugs are stinging or pain at the injection site, hiccoughs, nausea, vomiting, postoperative drowsiness and headache, and hypersensitivity reactions. Patients will be closely monitored and appropriate countermeasures will be taken as necessary.

General Anesthesia: General anesthesia may be used in some patients undergoing endoscopy and will be provided by CCMD and/or experienced anesthesiologists of the NIH CC. Common side effects include nausea, vomiting, mild allergic reactions, headache, and dizziness. Temporary confusion, lung infection, stroke, heart attack, or death are exceedingly rare side effects. Patients that undergo general anesthesia will be closely monitored during and after the procedure for adverse reactions.

Venous blood draw: Blood drawing may cause pain, bruising, lightheadedness, dizziness, possible fainting, local discomfort, bleeding, and, rarely, infection at the site where the needle is inserted. The amount of blood collected for research purposes under this protocol will not exceed the limits allowed for adult and pediatric research subjects by the NIH CC (http://cc-internal.cc.nih.gov/policies/PDF/M95-9.pdf). Additionally, at the time of enrollment, the study staff will ask each subject about their participation in other research studies to ensure the amount of blood drawn for research purposes does not exceed these guidelines.

Vaginal fluid collection using the Instead Softcup: Patient may experience pressure as the Instead Softcup is inserted into the vaginal cavity. The patient should not feel any discomfort during the secretion collection. The test is usually not painful. There is a risk of dislodging an IUD with the Instead Softcup, so vaginal fluid collection will NOT be done in patients with IUDs. There is also a risk of Toxic Shock Syndrome when the Instead Softcup is left in the vaginal

cavity for more than 12 hours. Patients will be instructed to remove the Instead Softcup after 1 to 2 hours.

Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED): APECED patients are hypoadrenal and therefore require stress-dose steroids for any procedure. The risks of inadequate steroid coverage are hypotension, circulatory collapse, and death. Patients will be closely monitored during steroid therapy, and any adverse reactions will be treated appropriately.

Photographs: Having pictures taken may be embarrassing to some people. These photographs may be published in medical journals, without identifying the participant. We will attempt to preserve the anonymity of the participant as much as possible, while providing the information needed to support the research being published. Participants may decline photographs or place any restrictions on their use. Participants will be given the opportunity to discuss this with the PI or AIs.

8.2 Potential Benefits

The individuals we will enroll on this study will be refractory or intolerant to standard non-intravenous treatment for mucocutaneous candidiasis infections. Patients may not directly benefit from participating in this study. However there is the potential benefit that access to this novel formulation of AMB may be effective treatment of the *Candida* infection and result in clinical improvement. The information obtained in this study may improve the investigators' understanding of the use of CAMB in treating people with refractory mucocutaneous candidiasis.

9 Research Use of Stored Human Samples, Specimens, or Data

- **Intended Use:** Samples and data collected under this protocol may be used to study drug levels in plasma, stool, urine, vaginal or salivary secretions to understand the pharmacodynamics of the study drug. All of the patients will be enrolled on other studies that allow for genetic studies, including whole exome sequencing, so genetic studies will not be performed as part of this study.

- **Storage:** Access to stored samples will be limited using a locked freezer located in a locked room with restricted access. Specifically, PK blood and data will be stored in the locked sample analysis/storage room (key required) of the Clinical Pharmacokinetics Research Laboratory inside of the Clinical Center Pharmacy Department, which is restricted by badge access to only pharmacy department employee. Stool, urine, vaginal and saliva samples will be stored in locked Freezer OP11 node 2 probe 88. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data. Blood, stool, urine and saliva samples will be sent to Lambda Therapeutic Research, Inc. (Toronto, Ontario M1L 4S4, Canada) for analysis. Vaginal samples will remain with the Fungal Pathogenesis Unit at NIH. PBMC specimen will be stored at the Neutrophil Monitoring Laboratory, Leidos Biomedical Research , Inc.

- **Tracking:** Samples will be tracked using a database located on a password-protected computer, which will be maintained by the investigators and their designees. Only investigators and their designees will have access to this database.

- **Disposition at the Completion of the Protocol:**

  - In the future, other investigators (both at NIH and outside) may wish to use these samples and/or data for research purposes. If the planned research falls within the category of “human subjects research” on the part of the NIH researchers, NIH IRB review and approval will be obtained. This includes the NIH researchers sending out coded and linked samples or data and getting results that they can link back to their subjects. Any clinical information shared about the sample would similarly require before IRB approval.

- **Reporting the Loss or Destruction of Samples/Specimens/Data to the IRB:**

  Any loss or unanticipated destruction of samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) that meets the definition of a reportable event will be reported to the NIH IRB according to NIH Human Research Protection Program (HRPP) Policy 801.

- Additionally, subjects may decide at any point not to have their samples stored. In this case, the principal investigator (PI) will destroy all known remaining samples and report what was done to both the subject and to the IRB. This decision will not affect the subject's participation in this protocol or any other protocols at NIH.

10 Remuneration Plan for Subjects

Subjects will be compensated for their time and inconvenience. Study subjects who complete all study procedures in a dosing cohort will receive $520 plus $200 for endoscopy (if indicated per protocol). Subjects who do not complete all study procedures will receive compensation based on the extent of their participation as follows: $200 for the in-patient initial dosing study point and $80 for the serial PK blood draw; $40 for the 24 hour admission PK study point and $80 for the serial PK blood draw; $30 for each of 4 outpatient blood draws; $200 for endoscopy, if indicated per protocol. There will be no compensation for the Extension phase of the study, although payment for travel-related expenses will be provided according to the NIAID Travel Policy. Payment will be issued following the end-of study visit. Volunteers who require additional dosing cohorts will receive compensation for the new cohort, as above.

11 Assessment of Safety

11.1 Toxicity Scale

We will utilize National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (MODIFIED) (Appendix A).

11.2 Recording/Documentation

At each contact with the subject, information regarding AEs will be elicited by appropriate questioning and examinations. All events, both expected/unexpected and related/unrelated will be recorded on a source document. Source documents will include: progress notes, laboratory reports, consult notes, phone call

summaries, survey tools, and data collection tools. Source documents will be reviewed in a timely manner by the research team. All reportable AEs that are identified will be recorded in CRIMSON. The start date, the stop date, the severity of each reportable event, and the PI's judgment of the AE's relationship and expectedness to the study agent/intervention will also be recorded in CRIMSON.

11.3 Reporting Procedures

11.3.1 Reporting to the NIH IRB

Reportable events will be tracked and submitted to the NIH IRB as per Policy 801 (Appendix F) and Policy 802 (Appendix G).

11.3.2 Reporting to the NIAID Clinical Director

The PI will report unanticipated problems (UPs), major protocol deviations, and deaths to the NIAID clinical director according to institutional timelines.

11.3.3 Specific Adverse Event Reporting Requirements to the Sponsor

11.3.3.1 Serious Adverse Event Reporting

Any SAE that occurs after the consent is signed until 4 weeks after the last dose must be reported to Medpace Clinical Safety ("MedpaceSafety") whether or not it is judged related to the investigational product. All serious adverse events that the investigator considers related to study drug occurring 4 weeks after the last dose must be reported Medpace Safety.

Serious Adverse Event (SAE)

A Serious Adverse Event is an AE that results in one or more of the following outcomes:

- death.
- a life-threatening (i.e., an immediate threat to life) event
- an inpatient hospitalization or prolongation of an existing

hospitalization (see note below for exceptions)

- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect.

NOTE: The following hospitalizations are not considered SAEs in this clinical study:

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- elective surgery planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

To report the SAE, fax or e-mail the completed SAE form to Medpace (fax number listed below) within 24 hours of awareness.

Medpace SAE reporting:

e-mail: medpace-safetynotification@medpace.com

Medpace Clinical Safety, US

Telephone: +1-800-730-5779, dial 3 **or** +1-513-579-9911, dial 3

Facsimile: +1-866-336-5320 **or** +1-513-570-5196

The Investigator will provide, at a minimum, the protocol number, subject's initials, subject number, date of the SAE, SAE term, and relationship to

investigational product. Information identifying the subject must be obliterated before transmitting to Medpace Safety.

The PI will notify the IRB of the SAE according to its requirements. An initial report followed promptly by a complete report will be forwarded to the IRB, or in accordance with the IRB policy.

11.3.3.2 Serious Adverse Event Follow-up

The subject will be observed and monitored carefully until

- the event resolves, or
- the event/condition has stabilized (e.g., in the case of persistent impairment), or
- the event returns to baseline, if a baseline value is available.

Within 24 hours of receipt of new information, the updated follow-up SAE form, along with any supporting documentation (e.g., subject discharge summary or autopsy reports), should be faxed to Medpace Clinical Safety. All efforts must be taken to obtain follow-up information promptly.

Follow-up information may consist of:

- A hospital discharge summary for subjects who are hospitalized or hospitalized over a prolonged period due to the SAE. If possible, the discharge summary should be obtained when it becomes available.
- A copy of the autopsy report, if a death occurs and an autopsy is performed, should be obtained if possible when it becomes available.

Any SAEs that are ongoing at the end of treatment or early termination should be followed as described above. These data should be recorded on the source documents and submitted to the designee on a SAE report form. For ongoing SAEs, the investigator must submit follow-up SAE reports to the safety designee regarding the subject's subsequent course until the case is closed.

11.4 Pregnancy

Patients who become pregnant while on study will be taken off the study drug. In addition, pregnancies occurring up to 4 weeks after last dose should be reported to Medpace Safety. We will assist, as may be appropriate, in referral for

pregnancy-related medical attention, including high-risk obstetrical referral if requested, and will ask that the patient follow up with us and consent to share information as may be appropriate regarding the course and outcome of the pregnancy. We will ask for the patient to return for the regularly scheduled clinic visits so we can monitor them for any toxicity during the pregnancy. We will follow up with the patient after delivery in order to report any further AEs.

The investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure In Utero form to the investigator for completion. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

11.5 Type and Duration of the Follow-up of Subjects after Adverse Events

Investigators will follow AEs until the event has resolved, the condition has stabilized, is well characterized, or referred to appropriate medical management, whichever comes first. Events and follow-up information occurring after the last visit should be recorded in the source documentation. Investigators are not obliged to solicit AEs after a subjects' final visit; however, if an investigator learns of an SAE that occurs within 4 weeks after the last dose, then an SAE report form should be submitted to Medpace Safety.

11.6 Pausing Rules for an Individual Subject

Pausing is the suspension of administration of study agent to a single subject until a decision is made whether or not to resume administration of the study agent.

The pausing criteria for a single subject in this study include any of the following:

- A subject experiences a Grade 3 laboratory event that is thought by the investigator to be possibly, probably or definitely related to study drug (see Appendix A)
- Any safety issue that the investigator determines should pause administration of a study agent to a single subject.

The PI will determine whether or not it is safe to resume administration of the study agent to the subject. A subject who does not resume CAMB will continue to be followed for safety.

11.7 Stopping Rules for an Individual Subject

A study subject will be discontinued from further study agent administration in the event of 1 or more of the following:

- Gastrointestinal toxicity (nausea/vomiting/diarrhea) that is interfering with the ability to perform regular every day activities.
- A subject experiences two Grade 3 events and/or one Grade 4 event that is possibly, probably, or definitely related to participation in the trial;
- SAE that is possibly, probably or definitely related to the study drug.
- Any laboratory abnormality, intercurrent illness, other medical condition or situation that occurs such that continued participation in the study would not be in the best interest of the subject.
- Any other events that the patient or investigators deems of clinical significance.

11.8 Halting Rules for the Protocol

The study will be halted (no new enrollments and no further administration of study drug) by the investigators and a report will be submitted to the IRB if 3 or more subjects experience one of the following in the 200 mg/day dosage level:

- serum potassium values of 3 mmol/L or less
- serum creatine value that is above 1.2 mg/dL and is 50% or more above the baseline value

The IRB, the NIAID, the sponsor, the Food and Drug Administration (FDA), or other government agencies, as part of their duties to ensure that research subjects are protected, may discontinue the study at any time. Subsequent review of serious, unexpected and related AEs by the Medical Monitor, SMC, IRB, the sponsor, the FDA, and other regulatory authorities may also result in suspension of further trial interventions/administration of study agent at a site. The FDA, other regulatory authorities, and the study sponsor retain the authority to suspend additional enrollment and study agent administration for the entire study as applicable.

11.9 Withdrawal Criteria for an Individual Subject

An individual patient will be withdrawn from the study for any of the following:

- An individual patient's decision. (The investigator should attempt to determine the reason for the patient's decision.)
- Non-compliance with study procedures to the extent that it is potentially harmful to the patient or to the integrity of the study data.
- A patient permanently loses capacity to provide informed consent.
- The investigator determines that continued participation in the study would not be in the best interest of the patient.

Patients who have withdrawn from the study before Day 14 will be replaced. If a patient is replaced, then all of their data will still be included for the safety assessment.

11.10 Safety Oversight

11.10.1 Safety Monitoring Committee

An independent safety monitoring committee (SMC) consisting of 3 individuals will review the study prior to initiation and then after 3 subjects have been on study drug for approximately 3 weeks. The SMC will then specify the next meeting point. The SMC will focus on subject safety and will include subject matter experts. The independent experts do not have direct involvement in the conduct of the study and have no significant conflicts of interest as defined by NIAID policy.

Prior to each SMC review, the PI will submit data as requested by the SMC. After each SMC review, a recommendation as to whether the study is to continue, be modified, or be terminated will be provided in a summary report. All SAEs, all UPs, and all IND Safety Reports will be reported by the PI to the SMC at the same time they are submitted to the IRB or IND sponsor. The SMC will be notified immediately if pausing, stopping, or halting rules are met, and the SMC will provide a recommendation for continuation, modification, or termination of the study. The PI will submit the written SMC summary reports with recommendations to the IRB.

12 Clinical Monitoring Structure

12.1 Site Monitoring Plan

An initiation meeting will be conducted by Matinas Biopharma Nanotechnologies, Inc. or an approved representative. At this meeting, the protocol and data collection procedures will be reviewed with the PI and all study staff.

Monitoring visits will be conducted during the study by Matinas Biopharma Nanotechnologies, Inc. or designee. The PI will make a reasonable amount of time available to the CRA on reasonable notice to assist with monitoring.

At each visit, the CRA will review CRIMSON data abstracts and source documents to ensure that all items have been completed and that the data provided are accurate and obtained in the manner specified in the protocol.

As per ICH-GCP 5.18 and FDA 21 CFR 312.50 clinical protocols are required to be adequately monitored. At the request of the NIAID Clinical Director this protocol monitoring for the NIH site will be conducted according to the “NIAID Intramural Clinical Monitoring Guidelines.” Monitors under contract to the NIAID/OCRPRO will visit the NIH site to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent documents and documentation of the ICF process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare abstracted information from CRIMSON data abstracts with individual subjects’

records and source documents (subjects' charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators are in compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections-OHRP), FDA, and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The investigator (and/or designee) will make study documents (e.g., consent forms, CRIMSON data abstracts and pertinent hospital or clinical records readily available for inspection by the local IRB, FDA, the site monitors, and the NIAID staff for confirmation of the study data.

A specific protocol monitoring plan will be discussed with the Principal Investigator and study staff. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status and regulatory obligations.

12.2 Auditing Procedures

In addition to the monitoring visits outlined above, an investigational site may undergo a quality assurance audit. Matinas Biopharma Nanotechnologies, Inc., its authorized representative, or a regulatory agency such as the FDA may conduct the audit. If a regulatory agency requests an audit of the study site, the Investigator is required to inform Matinas Biopharma Nanotechnologies, Inc. immediately.

13 Statistical Considerations

13.1 Study Hypotheses

CAMB will improve clinical symptoms of mucocutaneous candidiasis (OC/EC/VVC) in patients that are refractory or intolerant to standard non-

intravenous therapies.

13.2 Sample Size Justification

Sixteen patients will be accrued to the study. This sample size will provide 80% power to distinguish between true underlying improvement in clinical symptom rates of 5% and 25% using a 0.043 significance level. The 0.043 type I error rate will be used since the small sample size and yes/no endpoint do not allow for a 0.05 level test. The 0.043 level is as close to 0.05 as possible without being larger than 0.05.

The 5% rate with standard of care is based on historical observations at the clinical center that in this immune deficient population few if any patients have sustained improvement.

With 16 patients there will be a probability of 0.8 (80% power) of observing 3 or more responses if the true response rate with CAMB treatment is 25%. There will be a 0.043 (type I error rate) probability of observing 3 or more responses if the true response rate with CAMB is 5% (no better than current treatments).

Analysis Populations

The safety population will comprise all subjects who received at least one dose of investigational product.

13.3 Description of the Analyses

13.3.1 Efficacy Statistical Analysis

If 3 or more clinical improvements in symptoms are observed out of the 16 patients we will conclude there is promising evidence to continue studying CAMB. With this criteria there is a 0.043 probability of concluding CAMB is promising when the true rate of clinical improvement is 5% (no better than current treatments) and there is an 0.8 probability of concluding CAMB is promising when the true rate is 25% (improvement over current treatments).

If extra patients (up to the maximum of 20 patients) are accrued to the study the data will be analyzed to maintain type I error rate less than 0.05.

13.3.2 Safety Analysis

Safety analyses will include where appropriate, descriptive statistics, counts, and percentages.

Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by System Organ Class (SOC) and Preferred Term for each treatment group. All AEs will be captured after the first dose through the final visit or ET visit.

AEs will be summarized by presenting:

- The number and percentage of subjects experiencing any AE
- The number and percentage of subjects experiencing any AE by SOC
- The number and percentage of subjects experiencing any SAE
- The number and percentage of subjects experiencing any AE associated with study discontinuation

Clinical Laboratory Parameters

Clinical laboratory measurements (serum creatinine, potassium, CRP, ALT, AST) and changes from baseline to end-of-treatment will be summarized descriptively for each visit with the mean, median, standard deviation (SD), minimum, and maximum, by treatment group.

Vital Signs

Vital signs will be summarized descriptively for the mean, median, SD, minimum, and maximum by treatment group.

13.3.3 PK Analysis

Plasma drug levels will be determined predose and at 1 (± 5 minutes), 2 (± 5 minutes), 4 (± 15 minutes), 8 (± 15 minutes), 10 (± 15 minutes), 12 (± 15 minutes), and 24 hours (± 1 hour) postdose on Days 1 and 14 (all dosages), 21 (200 mg/day), 27 (400 and 800 mg/day), and 40 (800 mg/day). Blood samples will be processed to measure plasma concentrations via a validated LC-MS/MS assay. Twenty-four-hour urine collections will have total volume recorded and a 10-mL sample aliquoted to measure concentrations via a validated LC-MS/MS assay. Saliva collected at predose and at 8

(±3 hours) and 24 (±1 hours) hours postdose on Days 1 and 14 (± 3 days) of each dosage level will be analyzed to measure concentrations via LC-MS/MS assay. Stool samples will be collected during the 24 hours after the initial dose, and at Day 14 (± 3 days) days of each dosage. Vaginal secretions will be collected between 24-26 hours postdose on Days 1 and 14 (± 3 days) of each dosage level and will be analyzed to measure concentrations via LC-MS/MS assay. The stool and vaginal samples will be optional for subjects.

Blood, stool, urine and saliva samples will be analyzed by Lambda Therapeutic Research Inc. (460 Comstock Road, Toronto, Ontario, M1L 4S4, Canada) CAMB plasma PK parameters will be determined using noncompartmental methods with Phoenix® WinNonlin® software (version 6.03; Pharsight Corporation, Mountain View, CA). Maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) will be obtained directly by observation of the plasma concentration vs. time profiles. The apparent elimination rate constant (λZ) will be determined by calculating the absolute value of the slope of the log–linear regression of at least 2 points of the plasma concentration–time plot (when reported). The elimination half-life ($T_{1/2}$) will be calculated as 0.693/λZ (when reported). The steady-state area under the concentration vs. time curve (AUC) from time 0 to 24 hours postdose (AUC_{0-24}) will be calculated using the linear (up)/logarithmic (down) trapezoidal rule with a minimum of four quantifiable concentrations. Dose proportionality (linearity) will be assessed by comparison of geometric means of AUC and C_{max} PK parameters among dose levels. The percentage of total administered dose excreted in urine will be determined and used to calculate the renal elimination rate constant and renal clearance. Saliva levels will be reported as descriptive data.

14 Ethics/Protection of Human Subjects

14.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is an ongoing conversation between the human research subject and the researchers, which begins before consent is given and continues until the end of the subject's involvement in the research. Discussions about the research will provide essential information about the study and include purpose, duration,

experimental procedures, alternatives, risks, and benefits. Subjects will be given the opportunity to ask questions and have them answered.

The subjects will sign the informed consent document before undergoing any research procedures. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The researcher will document the signing of the consent form in the subject's medical record. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.1.1 Remote Consent Process

During the coronavirus disease 2019 pandemic, reconsent will be obtained remotely from the final enrolled participant.

The informed consent document will be sent via secure email or file transfer to the potential participant. An explanation of the study will be provided over the telephone or NIH-approved video conferencing platform (e.g., Zoom, Microsoft Teams) after the participant has had the opportunity to read the consent form. The participant can print the appropriate form to sign and date in ink, or they can sign and date digitally using a stylus or mouse.

The participant will return the signed and dated consent form to the consenting investigator, who will sign and date it with the date it was received. The consent form can either be printed and signed and dated in ink, or signed and dated digitally. A fully executed copy will be sent to the participant for their records.

The informed consent process will be documented on a progress note by the consenting investigator. The investigator will confirm that written consent has been obtained prior to initiating any study interventions.

14.2 Subject Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all records will be kept confidential to the extent provided by federal, state and local law. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitors and other authorized representatives of the Sponsor, representatives of the IRB, and/or regulatory agencies may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or Sponsor requirements.

Records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Only investigators will have access to the code key. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB, the FDA, NIAID, OHRP, or the sponsor's designee.

For subjects residing outside the local (Bethesda, MD) area, blood samples for safety labs (CBC with diff, Comprehensive BMP), may be drawn and processed at Quest Diagnostics, LabCorp, or by a primary care doctor. These samples may be labeled with a StudyID (i.e. Matinas MB70004), gender, and date of birth, as required by the local facility.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

15 Data Handling and Record Keeping

15.1 Data Capture and Management

Study data will be maintained in CRIMSON, and collected directly from subjects during study visits and telephone calls, or will be abstracted from subjects' medical records. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary to confirm the data abstracted for this study. Data entry into CRIMSON will be performed by authorized individuals. The Investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner.

15.2 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH GCP Guideline. Study records will be maintained by the PI in accordance with CFR 312.62 and in compliance with institutional, IRB, state, and federal medical records retention requirements, whichever is longest. All stored records will be kept confidential to the extent required by federal, state, and local law.

16 Scientific References

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Appendix A Toxicity Table

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE (MODIFIED)

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
Rx = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE1	**Mild**: Transient or mild discomfort (<48 hours); no medical intervention/therapy required
GRADE2	**Moderate**: Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE3	**Severe**: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE4	**Life-threatening**: Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event.

LABORATORY RANGES

Where discrepancies in the ULN and LLN of laboratory ranges occur between those included in this document and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade.

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4 gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/ mm^3	13,000-15,000 /mm^3	15,000-30,000/mm^3	>30,000 or <1,000 mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	---------
Activated Partial Thromboplastin (APTT)	1.01 -1.66 × ULN	1.67 - 2.33 × ULN	2.34 - 3 × ULN	> 3 × ULN
CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4

Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia(corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/Dl or abnormal calcium *with* life threatening arrhythmia or tetany

Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required
ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN

ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion
CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent symptomatic Rx required	unstable dysrhythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required

Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused
RESPIRATORY				
	Grade 1	Grade 2	Grade 3	Grade 4
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	Dyspnea requiring oxygen therapy

GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	Incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness, no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	Paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g. vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g. vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e. upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint destruction
Myalgia	Myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

SKIN				
	Grade 1	Grade 2	Grade 3	Grade 4
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	
SYSTEMIC				
	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	Anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy

Fever: oral	37.7 - 38.5° C or 100.0 - 101.5 °F	38.6 - 39.5 °C or 101.6 - 102.9 °F	39.6 - 40.5 °C or 103 - 105 °F	> 40 °C or > 105 °F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25-50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

Appendix B Schedule of Procedures/Evaluations

	Study Schedule (Days)																		
	Screening (-14 to -1)[a]	0	1[c]	2	4	7[b] (± 1)	14 (± 3)[c,d,m]	If escalating, move to next row. No visits until Day 21 if continuing on 200 mg.[d]							21[b] (± 3)	28 (± 3)	42[b] (± 3)		
			200-mg Dosage Phase																
							14 (± 3)[c]	15 (± 3)	17 (± 2)	20[b] (± 2)	27 (± 3)[c,e,m]	If escalating, move to next row. No visits until Day 34 if continuing on 400 mg.[e]			34[b] (± 3)	41 (± 3)	55[b] (± 3)		ET
							400-mg Dosage Phase												
											27 (± 3)[c]	28 (± 3)	30 (± 2)	33[b] (± 2)	40 (± 3) [c,m]	47[b] (± 3)	54 (± 3)	68[b] (± 3)	
											800-mg Dosage Phase								
Informed Consent	X																		
Medical/Medication History	X	X																	
Clinical Assessment/ Physical Exam	X	X	X[f]		X		X[f]		X		X[f]		X		X[f]		X		X
GYN Exam, if applicable		X					X				X				X		X		X
Endoscopy[g]	X																X		
Adverse Events and Concomitant Medications			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Acute, Hepatic, Mineral Panels	X	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing[i]	X		X[f]				X[f]				X[f]				X[f]		X		X
Plasma PK[j]			X				X				X				X		X[k]		
Urine PK[l]			X				X				X				X				
Saliva PK[m]			X				X				X				X				
Stool PK[l]			X				X				X				X				
OMC Pictures	X	X					X				X				X		X		X
Vaginal Secretion [n]		X		X				X				X			X[p]				
Microbiology (fungal culture)	X	X[h]					X				X				X		X		X
Stored Samples[o]Samples[l]		X					X				X				X		X		X

ET = early termination; PK = pharmacokinetics; PT/PTT = prothrombin/partial thromboplastin; X = to be performed.

a Screening data will be collected from other protocols on which patients are enrolled. If screening data are older than 14 days, then procedures will be conducted again under this protocol.

b For these timepoints the patient and investigator have the option of doing a phone interview and obtaining lab work at a local laboratory. A copy of the results should be sent to the investigator.

c On these days, patients will only receive the morning dose.

d If the patient is a clinical responder on Day 14 and the study drug is well tolerated, then they will continue with their dosage for another 14 days. If they are not a clinical responder but the study drug is well tolerated, then the dosage will increase to 400 mg/day.

e If the patient is a clinical responder on Day 27 and the study drug is well tolerated, then they will continue with their dosage for another 14 days. If they are not a clinical responder but the study drug is well tolerated, then the dosage will increase to 800 mg/day.

f On these days, clinical assessment, physical exam, and pregnancy testing will be conducted before the morning dose is administered.

g Patients with a diagnosis of esophageal candidiasis will undergo a clinically indicated endoscopic evaluation within 4 weeks before study drug initiation. These patients will also undergo a second, research-indicated endoscopy at end of treatment or within 4 weeks of clinical improvement, whichever occurs first.

h If these evaluations have been conducted for screening within 72 hours of Day 0, then they do not need to be repeated on Day 0.

i Urine or plasma. Patients of childbearing potential only.

j Blood for 24-hour PK analysis will be collected predose and at 1 (± 5 minutes), 2 (± 5 minutes), 4 (± 15 minutes), 8 (± 15 minutes), 10 (± 15 minutes), 12 (± 15 minutes), and 24 hours (± 1 hour) postdose. Patients will only receive the morning dose on the days that 24-hour PK samples are collected.

k At Days 28, 41 and 54 study visits (before the morning dose), samples will only be collected once. Samples will be used for trough PK (final) analysis and not a 24-hour PK analysis.

l Continuous collection of urine and stool samples throughout the designated 24-hour period. Collection of stool is optional.

m Saliva will be collected predose and at 8 (± 3 hours) and 24 (± 1 hours) hours postdose.

n Vaginal secretions will be collected at baseline and between 24-26 hours postdose. Sample collection will be voluntary

o Peripheral blood mononuclear cells. Sample collection will be voluntary

p Vaginal secretions will be collected between 24-26 hours postdose. Sample collection will be voluntary. This collection will be done on Day 41 of the 800mg dosing cohort.

q Option to enter the Extension study if clinical responder status obtained at 2 weeks at the highest tolerated dose at which patient responds.

Appendix C Blood Volumes for Specimen Collection

	Study Schedule (Days)																	
	Screening (-14 to -1)	0	1	2	4	7 (± 1)	14 (± 3)	If escalating, move to next row. No visits until Day 21 if continuing on 200 mg.							21 (± 3)	28 (± 3)	42 (± 3)
			200-mg Dosage Phase															
							14 (± 3)	15 (± 3)	17 (± 2)	20 (± 2)	27 (± 3)	If escalating, move to next row. No visits until Day 34 if continuing on 400 mg.			34 (± 3)	41 (± 3)	55 (± 3)
							400-mg Dosage Phase											
											27 (± 3)	28 (± 3)	30 (± 2)	33 (± 2)	40 (± 3)	47 (± 3)	54 (± 3)	68 (± 3)
											800-mg Dosage Phase							
	Volume (mL)																	
Hematology	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Acute, Hepatic, Mineral Panels	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Pregnancy Testing	4		4				4				4				4		4	
Plasma PK			48				48				48				48		6	
Stored Samples		10					10				10				10		10	
Daily Volume	11	17	59	7	7	7	69	7	7	11.5	69	7	7	7	69	7	27	7
Cumulative Volume 200-mg Dosage	11	28	87	94	101	108	177									184	211	218
Cumulative Volume 400-mg Dosage	11	28	87	94	101	108	177	184	191	198	267					274	301	308
Cumulative Volume 800-mg Dosage	11	28	87	94	101	108	177	184	191	198	267	274	281	288	357	364	391	398

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Appendix D Schedule of Procedures/Evaluations – Extension Study

	Extension Entry[1]	Bi-weekly Visits to NIH +/- 3 days) for first month after extension study entry[2]	Bi-weekly safety labs (every 2 weeks +/- 4 days) at NIH or local lab[3]	Monthly phone calls +/- 4 days (at 2 week interim between quarterly NIH visits)	Quarterly visits to NIH (every 12-weeks +/- 7days)[4]
Informed consent	x				
Clinical Assessment/Physical Exam	x	x	x		x
Adverse Events and Concomitant Medications, drug compliance	x	x	x	x	x
GYN Exam if applicable	x	x			x
Hematology (CBC/Diff)	x	x	x		x
Chemistry (Acute, Hepatic, Mineral Panels)	x	x	x		x
Urinalysis	x	x			x
Pregnancy Testing	x				x
Microbiology (fungal culture)	x	x			x
Stored Samples (serum & PBMC) [5]	x	x			x
Urine, plasma, stool, saliva and vaginal secretions[5]	x	x			x
OMC pictures	x				x

1. All procedures/evaluations for extension study entry are to be conducted during the last treatment visit of the primary study.
2. Bi-weekly visits to NIH will be performed in-person at NIH Clinical Center every 2-weeks during first month of the extension.

3. Bi-weekly lab draws can be done at the NIH Clinical Center or at the home laboratory. If the visits are conducted at NIH a clinical assessment/physical exam will be performed along with adverse event and concomitant medication collection.
4. After the first month of the extension, in person visits to the NIH Clinical Center will be quarterly. The 3-month visits will go out to 60 months from the Extension Entry visit. If a patient chooses to terminate the Extension study prior to the 60-month visit, the same monthly procedures/evaluations will be conducted at the Early Termination visit as the Monthly visits.
5. These collections are optional.

Appendix E Blood Volumes for Specimen Collection – Extension Study

Study Week	Visit	Hematology (3)	Acute, Hepatic, Mineral Panel (4)	Pregnancy Testing (4)	Stored Samples (10)	Plasma (6)	Total Per Visit (mL)	Cummulative Total (mL)
Week 2	Biweekly at NIH	3	4		10	6	23	23
Week 4	Monthly at NIH	3	4	4	10	6	27	50
Week 6	Bi-weekly	3	4				7	57
Week 8	Bi-weekly	3	4				7	64
Week 10	Bi-weekly	3	4				7	71
Week 12	Bi- weekly	3	4				7	78
Week 14	Bi-weekly	3	4				7	85
Week 16	Quarterly at NIH	3	4	4	10	6	27	112
Week 18	Bi-weekly	3	4				7	119
Week 20	Bi-weekly	3	4				7	126
Week 22	Bi-weekly	3	4				7	133
Week 24	Bi-weekly	3	4				7	140
Week 26	Bi-weekly	3	4				7	147
Week 28	Bi-Quarterly NIH	3	4	4	10	6	27	174
Week 30	Bi-weekly	3	4				7	181
Week 32	Bi-weekly	3	4				7	188
Week 34	Bi-weekly	3	4				7	195
Week 36	Bi-weekly	3	4				7	202
Week 38	Bi-weekly	3	4				7	209
Week 40	Quarterly NIH	3	4	4	10	6	27	236
Week 42	Bi-weekly	3	4				7	243
Week 44	Bi-weekly	3	4				7	250
Study Week	Visit	Hematology (3)	Acute, Hepatic, Mineral Panel (4)	Pregnancy Testing (4)	Stored Samples (10)	Plasma (6)	Total Per Visit (mL)	Cummulative Total (mL)
Week 46	Bi-weekly	3	4				7	257
Week 48	Bi-weekly	3	4				7	264

Week 50	Bi-weekly	3	4				7	271
Week 52	Quarterly NIH	3	4	4	10	6	27	298
Week 54	Bi-weekly	3	4				7	305
Week 56	Bi-weekly	3	4				7	312
Week 58	Bi-weekly	3	4				7	319
Week 60	Bi-weekly	3	4				7	326
Week 62	Bi-weekly	3	4				7	333
Week 64	Quarterly NIH	3	4	4	10	6	27	360
Week 66	Bi-weekly	3	4				7	367
Week 68	Bi-weekly	3	4				7	374
Week 70	Bi-weekly	3	4				7	381
Week 72	Bi-weekly	3	4				7	388
Week 74	Bi-weekly	3	4				7	395
Week 76	Quarterly NIH	3	4	4	10	6	27	422
Week 78	Bi-weekly	3	4				7	429
Week 80	Bi-weekly	3	4				7	436
Week 82	Bi-weekly	3	4				7	443
Week 84	Bi-weekly	3	4				7	450
Week 86	Bi-weekly	3	4				7	457
Week 88	Quarterly NIH	3	4	4	10	6	27	484
Week 90	Bi-weekly	3	4				7	491
Week 92	Bi-weekly	3	4				7	498
Study Week	Visit	Hematology (3)	Acute, Hepatic, Mineral Panel (4)	Pregnancy Testing (4)	Stored Samples (10)	Plasma (6)	Total Per Visit (mL)	Cumulative Total (mL)
Week 94	Bi-weekly	3	4				7	505
Week 96	Bi-weekly	3	4				7	512
Week 98	Bi-weekly	3	4				7	519
Week 100	Quarterly NIH	3	4	4	10	6	27	546
Week 102	Bi-weekly	3	4				7	553

Week 104	Bi-weekly	3	4				7	560
Week 106	Bi-weekly	3	4				7	567
Week 108	Bi-weekly	3	4				7	574
Week 110	Bi-weekly	3	4				7	581
Week 112	Quarterly NIH	3	4	4	10	6	27	608
Week 114	Bi-weekly	3	4				7	615
Week 116	Bi-weekly	3	4				7	622
Week 118	Bi-weekly	3	4				7	629
Week 120	Bi-weekly	3	4				7	636
Week 122	Bi-weekly	3	4				7	643
Week 124	Quarterly NIH	3	4	4	10	6	27	670
Week 126	Bi-weekly	3	4				7	677
Week 128	Bi-weekly	3	4				7	684
Week 130	Bi-weekly	3	4				7	691
Week 132	Bi-weekly	3	4				7	698
Week 134	Bi-weekly	3	4				7	705
Week 136	Quarterly NIH	3	4	4	10	6	27	732
Week 138	Bi-weekly	3	4				7	739
Week 140	Bi-weekly	3	4				7	746
Study Week	Visit	Hematology (3)	Acute, Hepatic, Mineral Panel (4)	Pregnancy Testing (4)	Stored Samples (10)	Plasma (6)	Total Per Visit (mL)	Cumulative Total (mL)
Week 142	Bi-weekly	3	4				7	753
Week 144	Bi-weekly	3	4				7	760
Week 146	Bi-weekly	3	4				7	767
Week 148	Quarterly NIH	3	4	4	10	6	27	794
Week 150	Bi-weekly	3	4				7	801
Week 152	Bi-weekly	3	4				7	808
Week 154	Bi-weekly	3	4				7	815
Week 156	Bi-weekly	3	4				7	822
Week 158	Bi-weekly	3	4				7	829

Study Week	Visit	Hematology (3)	Acute, Hepatic, Mineral Panel (4)	Pregnancy Testing (4)	Stored Samples (10)	Plasma (6)	Total Per Visit (mL)	Cumulative Total (mL)
Week 160	Quarterly NIH	3	4	4	10	6	27	856
Week 162	Bi-weekly	3	4				7	863
Week 164	Bi-weekly	3	4				7	870
Week 166	Bi-weekly	3	4				7	877
Week 168	Bi-weekly	3	4				7	884
Week 170	Bi-weekly	3	4				7	891
Week 172	Quarterly NIH	3	4	4	10	6	27	918
Week 174	Bi-weekly	3	4				7	925
Week 176	Bi-weekly	3	4				7	932
Week 178	Bi-weekly	3	4				7	939
Week 180	Bi-weekly	3	4				7	946
Week 182	Bi-weekly	3	4				7	953
Week 186	Quarterly NIH	3	4	4	10	6	27	980
Week 188	Bi-weekly	3	4				7	987
Week 190	Bi-weekly	3	4				7	994
Week 192	Bi-weekly	3	4				7	1001
Week 194	Bi-weekly	3	4				7	1008
Week 196	Bi-weekly	3	4				7	1015
Week 198	Quarterly NIH	3	4	4	10	6	27	1042
Week 200	Bi-weekly	3	4				7	1049
Week 202	Bi-weekly	3	4				7	1056
Week 204	Bi-weekly	3	4				7	1063
Week 206	Bi-weekly	3	4				7	1070
Week 208	Bi-weekly	3	4				7	1077
Week 210	Quarterly NIH	3	4	4	10	6	27	1104
Week 212	Bi-weekly	3	4				7	1111
Week 214	Bi-weekly	3	4				7	1118
Week 216	Bi-weekly	3	4				7	1125
Week 218	Bi-weekly	3	4				7	1132

Study Week	Visit	Hematology (3)	Acute, Hepatic, Mineral Panel (4)	Pregnancy Testing (4)	Stored Samples (10)	Plasma (6)	Total Per Visit (mL)	Cumulative Total (mL)
Week 220	Bi-weekly	3	4				7	1139
Week 222	Quarterly NIH	3	4	4	10	6	27	1166
Week 224	Bi-weekly	3	4				7	1173
Week 226	Bi-weekly	3	4				7	1180
Week 228	Bi-weekly	3	4				7	1187
Week 230	Bi-weekly	3	4				7	1194
Week 232	Bi-weekly	3	4				7	1201
Week 234	Quarterly NIH	3	4	4	10	6	27	1228
Week 236	Bi-weekly	3	4				7	1235
Week 238	Bi-weekly	3	4				7	1242
Week 240	Bi-weekly	3	4				7	1240
Week 242	Bi-weekly	3	4				7	1256
Week 244	Bi-weekly	3	4				7	1263
Week 246	Quarterly NIH	3	4	4	10	6	27	1290
Week 248	Bi-weekly	3	4				7	1297
Week 250	Bi-weekly	3	4				7	1304
Week 252	Bi-weekly	3	4				7	1311
Week 254	Bi-weekly	3	4				7	1318
Week 256	Bi-weekly	3	4				7	1325
Week 258	NIH	3	4	4	10	6	27	1352

Appendix F NIH SOP 801

Policy

1. Purpose

1.1. This policy outlines the requirements for the reporting research-related events to the Institutional Review Board (IRB).

2. Scope

2.1. This policy applies to all NIH investigators conducting human subjects research (also referred to in this policy as "studies") and to the Office of Human Subjects Research Protections (OHSRP).

2.2. This policy applies to investigators not covered by the NIH FWA when the NIH is the Reviewing IRB for human subjects research conducted by these investigators.

3. Policy

3.1. For all human subjects research in which an NIH IRB is the Reviewing IRB, NIH Principal Investigators (PIs) and, as applicable, non-NIH Site PIs/Lead Investigators (further referred to as non-NIH investigators), are required to ensure that all reportable events, as defined in this policy, are reported to the OHSRP office of Compliance and Training within the time frames as specified in this policy.

3.1.1. The NIH Principal Investigators (PIs)/designee and, as applicable, non-NIH Investigators must report events to the OHSRP office of Compliance and Training via the Reportable Event Submission Form (REF) in NIH iRIS in accordance with Section 5.1, whether the events occur at the NIH or a non-NIH site;

3.2. For human subjects research when the Reviewing IRB is not an NIH IRB, NIH PIs/Lead investigators (further referred to as NIH PI(s) to include NIH PIs, NIH Site PIs in the case of multisite research, and NIH AIs participating in a collaborative research protocol with a

non-NIH PI) are required to ensure that the reporting requirements of the Reviewing IRB are followed by NIH staff.

3.2.1. When the Reviewing IRB is a non-NIH IRB, and the event occurred at an NIH site, the NIH PI must report the event to the Reviewing IRB in accordance with that IRB's instructions, and also to the OHSRP office of Compliance and Training via the REF in NIH iRIS within 7 calendar days of the NIH PI becoming aware of the event;

3.2.2. When the Reviewing IRB is a non-NIH IRB, and the event occurred at a non-NIH site, the NIH PI/NIH lead Investigator is required to ensure that the reporting requirements of the Reviewing IRB are followed. The investigator does not also report these events to the OHSRP office of Compliance and Training.

3.3. Additional reporting may also be required as specified by an NIH Institute/Center (IC) or other NIH policy.

3.4. This policy's reporting requirements are in addition to the requirements of regulatory agencies (such as the FDA) and/or any institutionally agreed-upon requirements, e.g., with study sponsors or through reliance agreements.

4. Definitions

4.1. Adverse Event (AE) - Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. In the context of FDA-required reporting, an AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

4.2. NIH Investigator - An NIH federal employee (intramural or extramural) who is conducting human subjects research on behalf of the NIH. Additionally, this designation includes an

investigator who is not an NIH federal employee but who is conducting human subjects research while working at an NIH site with an NIH employee. These researchers may include Guest Researchers, Special Volunteers, contractors (subject to the terms of the contract), Intramural Research and Cancer Research Training Awardees and colleagues from academia and industry who are not Special Government Employees (SGEs) or Intergovernmental Personnel Act appointee.

4.3. Non-Compliance - Failure of investigator(s) to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research, or the requirements or determinations of the IRB, whether intentional or not. For the purposes of this policy, failure of subjects to comply with the research protocol does not represent non-compliance unless that failure is due to an action or omission of a member of the research team, for example, the failure to give adequate instruction to the subject.

4.3.1. Serious non-compliance - Non-compliance, whether intentional or not, that results in harm or otherwise materially compromises the rights, welfare and/or safety of the subject. Non-compliance that materially effects the scientific integrity or validity of the research may be considered serious non-compliance, even if it does not result in direct harm to research subjects.

4.3.2. Continuing non-compliance - A pattern of recurring non-compliance that either has resulted, or, if continued, may result in harm to subjects or otherwise materially compromise the rights, welfare and/or safety of subjects, affect the scientific integrity of the study or validity of the results. The pattern may comprise repetition of the same non-compliant action(s), or different non- compliant events. Such non-compliance may be unintentional (e.g. due to lack of understanding, knowledge, or commitment), or intentional (e.g. due to deliberate choice to ignore or compromise the requirements of any applicable regulation, organizational policy, or determination of the IRB).

4.4. Protocol Deviation (PD) - Any change, divergence, or departure from the IRB-approved research protocol.

4.4.1. Major Deviations - Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact, the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.

4.4.2. Minor Deviations - Deviations that do not have the potential to negatively impact the rights, safety, or welfare of subjects or others, or the scientific integrity or validity of the study.

4.5. Reportable Event - An event that occurs during the course of human subjects research that requires notification to the IRB. For the purposes of this policy, reportable events include non-compliance and unanticipated problems involving risks to subjects or others (also referred to as UPs), major deviations, deaths related or possibly related to research activities and new information that might affect the willingness of subjects to enroll or continue participation in the study.

4.6. Reviewing IRB - The IRB responsible for reviewing human subjects research and determining that the research meets the required criteria for approval under the HHS regulatory requirements at 45 CFR 46 and, as applicable, the pertinent Subparts of 21 CFR.

4.7. Serious Adverse Event (SAE) -is any Adverse Event that:

- Results in death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Results in inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect; OR
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the 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).

In IND-regulated research, this term is used synonymously with *serious*

suspected adverse reaction. (See 21 CFR 312.32(a) for the FDA definition.)

4.8. Unanticipated (Unexpected) - An experience that was not expected or previously observed, or is not consistent in nature, severity, or frequency with existing risk information, such as in the investigator's brochure, device manual, research protocol, consent form, or other available information (e.g., IND application for an investigational drug or IDE application for an investigational device). Interchangeable with "unexpected". This includes an event or problem occurring in one or more subjects in a research study that is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the subject experiencing the event/problem.

4.9. Unanticipated adverse device effect - means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application),

or any other unanticipated serious problem associated with a device that relates to the right, safety, or

welfare of subjects.

4.10. Unanticipated Problem Involving Risks to Subjects or Others (UP) - Any incident, experience, or outcome that meets all the following criteria:

4.10.1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; and

4.10.2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research), and

4.10.3. Suggests that the research places subjects, or others (which may include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or expected.

5. Responsibilities and Requirements

5.1. Responsibilities of investigators:

5.1.1. The PI must ensure that all AEs and SAEs are appropriately identified, tracked and recorded, according to the IRB-approved protocol, data and safety monitoring plan, and in accordance with any additional NIH, regulatory, IC-specific and/or study sponsor requirements. (Policy 506 Data and Safety Monitoring)

5.1.2. The NIH Principal Investigators (PIs)/designee and, as applicable, non-NIH Investigators, must ensure that the following events are reported within the time frames specified below. (See *Appendix 1: Investigator Reporting Requirements and Timeframes* for tabular view of these requirements)

5.1.2.1. Non-compliance: Any actual or suspected non-compliance by any investigator or entity associated with the protocol must be reported by the NIH PI/designee within 7 calendar days of any investigator or individual associated with the protocol first becoming aware, unless otherwise indicated in this policy. Please refer to policy 802 Non-compliance in Human Subjects Research.

5.1.2.1.1. Non-NIH IRB Determinations of serious and/or continuing non-compliance about an NIH investigator: If the NIH is relying on a non-NIH IRB and the Reviewing IRB makes a determination of serious and/or

continuing non-compliance regarding an NIH investigator, then, even if the determination has already been provided to OHSRP either directly or via the NIH Institutional Official (IO)/designee, the NIH PI/designee must report this in iRIS within 7 calendar days of any member of the research team being notified of the determination by the Reviewing IRB. The NIH PI must provide the OHSRP office of Compliance and Training with documentation from the Reviewing IRB unless this documentation has already been provided directly to the office by the Reviewing IRB or via the IO.

5.1.2.2. Major Deviation: A deviation must be reported within 7 calendar days of an investigator becoming aware of an actual or suspected deviation. Although protocol deviations are also non-compliance, these should only be reported once as deviations.

5.1.2.3. Unanticipated Problem (UP): A UP must be reported within 7 calendar days of an investigator becoming aware of the actual or suspected UP.

5.1.2.4. Death: Any death of a research subject that is possibly, probably or definitely related to the research must be reported within 24 hours of an investigator becoming aware of the death.

5.1.2.5. New information that might affect the willingness of a subject to enroll or remain in the study should be reported within 7 calendar days of an investigator first becoming aware.

5.1.2.6. Any suspension or termination of research activities, including holds on new enrollment, placed upon the research by the study sponsor, NIH or IC leadership, or any regulatory agency must be reported within 7 calendar days of an investigator becoming aware.

5.1.2.7. Investigators must provide the following information to the IRB in summary format at the time of continuing review, or when otherwise specifically requested by the IRB or the OHSRP office of Compliance and Training.

5.1.2.7.1. Minor protocol deviations.

5.1.2.7.2. Adverse events and Serious Adverse Events that do not meet the definition of an UP.

5.1.3. For FDA regulated studies, investigators are required to report events to the study sponsor as described in the protocol and to immediately (i.e., no longer than 10 days) report SAEs or UADEs to the study sponsor and, if also an actual or suspected UP, to the IRB within 7 calendar days of an investigator becoming aware.

5.2. Responsibilities of the OHSRP Office of Compliance and Training and the IRB(s):

5.2.1. When NIH is the Reviewing IRB, the OHSRP office of Compliance and Training is responsible for the following:

5.2.1.1. Conducting initial evaluation and triage of all reportable events submitted using iRIS.

5.2.1.2. In consultation, as needed, with the OHSRP Director, IRBO Director, and/or Executive Chair, determining if any reported event requires immediate action to protect the rights, safety or welfare of research subjects and if so, communicating such actions to the Principal Investigator and the IRB.

5.2.1.3. Referring potentially serious and/or continuing non-compliance to the Research Compliance Review Committee (RCRC).

5.2.1.4. Referring reported UPs to the convened IRB for determination and review of any proposed changes to the protocol or consent made by the PI in response to the UP.

5.2.1.5. Reporting to OHRP and, as applicable, FDA, all NIH IRB determinations of serious and/or continuing non-compliance, UPs, or NIH IRB suspensions or terminations of IRB approval within 30 days of the submission of the reportable event and/or will make interim reports in advance of the IRB's final determination as necessary.

5.2.2. When NIH is the Reviewing IRB, the RCRC, as a duly constituted IRB, is responsible for the following:

5.2.2.1. Reviewing possible serious and/or continuing non-compliance occurring within studies under the NIH IRB's purview.

5.2.2.2. Determining whether serious and/or continuing non-compliance occurred, and evaluating the adequacy of any proposed corrective action. (See Policy 802 Non-compliance in Human Subjects Research).

5.2.3. For studies in which the reviewing IRB is a non-NIH IRB, the regulatory responsibility for reporting to federal agencies lies with the Reviewing IRB unless otherwise specified in the reliance agreement.

6. References

6.1. Federal Regulations

DHHS: 45 CFR 46

FDA: 21 CFR parts 50, 56, 312 and 812

6.2. NIH Policies

Policy 506 Data and Safety Monitoring

Policy 802 Non-Compliance in Human Subjects Research

6.3. Guidance

E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1):Guidance for Industry

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others (2007)

7. Appendices:

7.1. **Appendix 1:** Investigator Reporting Requirements and Timeframes

8. Revision History: N/A

8.1. **Supersedes Date:** 07/01/2019

SOP 16 Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations

V.4 dated 3/14/2016

V.3 dated 2/24/2016

V.4 dated 2/26/14 (form only, note out of order versioning)

V.2 dated 10/01/2013 (form only)

V.1 dated 6/11/2013

V.1 dated 6/11/2013

Appendix 1: Principal Investigator/Designee Reporting Requirements and Timeframes

Investigator status	**NIH IRB is Reviewing IRB**	**Non-NIH IRB is Reviewing IRB**

NIH PI, or as applicable, the NIH lead site investigator	• Report the following events to the NIH IRB within 7 calendar days of any investigator first becoming aware*
	  o Actual or suspected non-compliance
	  o Actual or suspected Major deviations
	  o Actual or suspected Unanticipated Problems (UPs)
	  o New information that might affect the willingness of a subject to enroll or remain in the study
	  o Suspension or termination of research activities, including holds on new enrollment, placed upon the research by the study sponsor, NIH or IC leadership, or any regulatory agency
	• Death of a research subject that is possibly, probably or definitely related to the research must be reported within 24 hours of the investigator becoming aware of the death
	• For FDA regulated studies, report events to the study sponsor as described in the protocol and immediately report (i.e., no longer than 10 days) SAEs or UADEs to the study sponsor and, if also an actual or suspected UP, to the IRB within 7 calendar days of the investigator becoming aware.
	Report minor deviation and adverse events and serious adverse events that are not UPs
		• Report events to the Reviewing IRB as per its policy
		• If event occurs at an NIH site, also report to the Reviewing IRB and the OHSRP office of Compliance and Training within 7 calendar days*
		• For FDA regulated studies, report events to the study sponsor as described in the protocol and immediately report (i.e., no longer than 10 days) SAEs or UADEs to the study sponsor and, if also a UP, to the IRB within 7 calendar days.
		• Report any determinations by the non-NIH Reviewing IRB of serious and/or continuing non-compliance by an NIH investigator in iRIS within 7 calendar days.* Also, provide the OHSRP office of Compliance and Training with documentation from the Reviewing IRB unless this documentation has already been provided directly to the office by the Reviewing IRB or via the

	at the time of continuing review, or when otherwise specifically requested by the IRB or the OHSRP office of Compliance and Training.	Institutional Official.
Non-NIH Investigator	Requirements for reporting events to the NIH IRB are the same as those for the NIH investigators as defined above** (Non-NIH investigators should consult their institution's policies if local reporting is also required.)	Report events to the Reviewing IRB as per its policy

*Submit a Reportable Event Form in iRIS

** Mode of submission by the Non-NIH Investigator will be determined by the IRBO

Appendix G NIH SOP 802

Policy

A. Purpose

1. The purpose of this policy is to describe the process for the investigation and resolution of allegations of non-compliance.

B. Scope

1. This policy applies to NIH investigators conducting human subjects research reviewed by an NIH IRB.
2. This policy applies to investigators not covered by the NIH FWA when the NIH is the Reviewing IRB for human subjects research conducted by these investigators.
3. This policy applies to the OHSRP and its offices and the NIH IRB.
4. This policy also applies to persons or entities within the NIH who suspect possible non- compliance in the conduct of human subjects research.

C. Policy

1. NIH investigators are required to follow all applicable laws, regulations, and NIH institutional policies governing the protection of human subjects in research. Non-NIH investigators who are under the jurisdiction of the NIH IRBs, must follow applicable laws, regulations and NIH policies as they relate to the protection of human subjects in research.
2. Investigators, any member or component of the NIH Human Research Protection Program (HRPP), or any individual or entity within the NIH who suspects possible non-compliance in the conduct of human subjects research, is required to report such an occurrence consistent with this policy.
3. Allegations may be made anonymously and will be investigated to the extent possible.
4. The identity of complainants will be kept confidential to the extent possible.
5. Allegations from subjects or their family members that relate to possible non-compliance may also be reported.
6. All allegations of non-compliance should be reported to the OHSRP office of Compliance and Training (see Policy 801 Reporting Research Events).
7. Allegations of non-compliance will be investigated in a fair and timely manner, and the respondent will be given an opportunity to respond to any allegation of non-compliance before a final determination is made.
8. Allegations related to possible non-compliance of an IRB will be referred to the Deputy Director for Intramural Research (DDIR) who will determine the

process for investigating the allegation.

9. For all protocols in which the research was conducted under the jurisdiction of the NIH IRBs, the Research Compliance Review Committee (RCRC) has the final authority to determine whether there is non-compliance and, if so, whether it is serious and/or continuing.
10. When NIH is relying on an external IRB, NIH investigators must follow the policies of the Reviewing IRB for reporting possible non-compliance. Please see Policy 801 Reporting Research Events for additional NIH reporting requirements.
11. The individual(s) who alleges non-compliance (Complainant) related to human subjects research will be informed, upon request, whether the investigation is continuing or completed. Additional information will be provided consistent with federal law and policy.
12. Allegations of non-compliance made in good faith will not reflect negatively on the reporting individual, nor lead to reprisal against that individual.

D. Definitions

1. *Allegation of Non-Compliance (also "allegations")* - A disclosure of possible non- compliance through any means of communication (e.g., by written or oral statement) to an NIH official. This may include concerns from research participants, investigators, staff, IRB members, reports from audits, and discoveries made during review of other human subjects issues, such as protocol deviations. It does not include self-reporting by the PI/designee to the IRB, using a reportable event form submitted in iRIS.
2. *Complainant* - A person who makes an allegation of non-compliance.
3. *NIH Investigator* - An NIH federal employee (intramural or extramural) who is conducting human subjects research on behalf of the NIH. Additionally, this designation includes an investigator who is not an NIH federal employee but who is conducting human subjects research while working at an NIH site with an NIH employee. These researchers may include Guest Researchers, Special Volunteers, contractors (subject to the terms of the contract), Intramural Research and Cancer Research Training Awardees and colleagues from academia and industry who are not Special Government Employees (SGEs) or Intergovernmental Personnel Act appointee.
4. *Non-Compliance* - Failure of investigator(s) to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research, or the requirements or determinations of the IRB, whether the failure is intentional or not. For the purposes of this policy, failure of subjects to comply with the research protocol does not represent non- compliance unless that failure is due to an action or omission of a member of the research team, for example, the failure to give adequate instruction to the subject.
    - Serious non-compliance - Non-compliance, whether intentional or not, that results in harm or otherwise materially compromises the rights, welfare and/or safety of the subject. Non-compliance that materially affects the scientific integrity or validity of the research may be considered serious non-compliance, even if it does not result in direct harm to research subjects.

- Continuing non-compliance - A pattern of recurring non-compliance that either has resulted, or, if continued, may result in harm to subjects or otherwise materially compromise the rights, welfare and/or safety of subjects, affect the scientific integrity of the study or validity of the results. The pattern may comprise repetition of the same non- compliant action(s), or different non-compliant events. Such non- compliance may be unintentional (e.g. due to lack of understanding, knowledge, or commitment), or intentional (e.g. due to deliberate choice to ignore or compromise the requirements of any applicable regulation, organizational policy, or determination of the IRB).

5. *(The) OHSRP office of Compliance and Training* - The component of OHSRP responsible for review, management, and required reporting of problems occurring during the conduct of IRP human subjects research (HSR). This component also conducts non-compliance inquiries as well as QA/QI Reviews of NIH IRBs. This component also provides education and training related to human subjects protections, IRB policies and procedures for HRPP investigators, research staff, and the NIH IRB.
6. *Reliance Agreement* - An agreement between the NIH and one or more sites involved in the same cooperative research that assigns IRB regulatory responsibilities to a specified IRB. This is sometimes referred to as an IRB Authorization Agreement.
7. *Research Compliance Review Committee (RCRC)* - A duly established NIH IRB that adheres to the membership and committee requirements described in *Policy 302-IRB Membership and Composition* and *Policy 402-IRB meetings*. The RCRC primarily reviews allegations of non-compliance that have been deemed by the office of Compliance and Training to be both credible and potentially serious and/or continuing. As a duly convened committee, the RCRC may exercise the full authority of an IRB including suspension or termination of IRB approval of research.
8. *Respondent* - The investigator or entity, if any, against whom an allegation of non- compliance is made.

E. Responsibilities and Requirements

1. Investigators are required to follow all applicable laws, regulations, and NIH institutional policies governing the protection of human subjects in research. Non-NIH investigators who are under the jurisdiction of the NIH IRB, must follow applicable laws, regulations and NIH policies as they relate to governing the protection of human subjects in research.
2. Additionally, any member or component of the NIH Human Research Protection Program (HRPP), or any individual or entity within the NIH who suspects possible non- compliance in the conduct of human subjects research, is required to report such an occurrence. This must be reported in a timely manner to the office of Compliance and Training.
3. The Respondent and any involved person or entity are expected to fully cooperate with any investigation of non-compliance and provide any requested information and/or materials to the office of Compliance and Training, the IC, NIH Office of the Director (OD), or any other authorized party.
4. When an NIH IRB is the Reviewing IRB, the office of Compliance and Training is responsible for conducting the preliminary review of allegation of non-compliance, in consultation with, as necessary, the OHSRP Director, IRBO Director and/or the Executive Chair.
    a. The office of Compliance and Training will make a preliminary determination for the HRPP as to whether the allegation is credible (e.g., has a basis in fact) and falls within the scope of human subjects protections and, if so, whether the allegation of non-compliance, if true, is potentially serious and/or continuing.
        I. If allegations meet these criteria, the respondent will be notified of the allegations. The office of Compliance and Training will refer allegations of non-compliance deemed by it to be potentially serious and/or continuing to the RCRC. This will occur whether the protocol is open or not at the time of the allegation.
        II. If the answer to any of these criteria is "no," then the investigation will not proceed to consideration by the RCRC and the respondent will be notified.
        III. Possible non-compliance relating to concerns outside the scope of human subjects protections may be referred to the appropriate office for further review (e.g. matters related to possible scientific misconduct will be forwarded to the NIH Agency Intramural Research Integrity Officer (AIRIO)).
    b. In consultation with the OHSRP Director, IRBO Director and/or the Executive Chair, the office of Compliance and Training is responsible for determining for OHSRP if immediate steps are necessary to protect the rights, welfare and safety of subjects and communicate this to the RCRC and the PI.
        I. Administrative holds may also be placed on the research by the study sponsor, OD or NIH Institute or Center (IC) leadership, or any regulatory agency.
5. The RCRC is responsible for reviewing possible serious or continuing non-compliance in human subjects research for which an NIH IRB is the Reviewing IRB that has been referred from the office of Compliance and

Training. The RCRC has the final authority to determine whether there is non- compliance that is serious and/or continuing and to determine corrective action.

a. On behalf of the RCRC, the office of Compliance and Training is responsible for coordinating any investigation of an allegation of non-compliance, in consultation with the Director of OHSRP, the Director of IRBO and/or the Executive Chair of the NIH IRB. Additional resources will be requested from the HRPP and IC leadership as needed.

b. A written report will be prepared by office of Compliance and Training describing the possible non-compliance, evidence examined, and summary or source documents (if pertinent) of the investigation. The report will be provided to the RCRC and the respondent.

c. The respondent will be provided an opportunity to address the RCRC in person if they so choose and/or provide a written response.

d. The RCRC will make the final determination regarding non-compliance and if it is serious and/or continuing. The determination

will be provided in writing to the respondent, as well as to the Director OHSRP, IRBO Director, the DDIR, and the relevant IC CD.

I. When the NIH IRB(s) is the Reviewing IRB for a multi-center study, reporting to non-NIH sites will be governed by the terms of the reliance agreement.

e. As appropriate, the investigator with assistance of their IC, as needed, will initiate corrective action.

I. As part of its deliberations, the RCRC will determine the adequacy of any proposed corrective actions.

II. As a duly convened IRB, the RCRC may require modifications to any proposed corrective action as a condition for continued approval of research, for example, continued monitoring, notification to past research subjects, or reconsent of current subjects when the investigation results in information that might impact the subjects' willingness to continue participation. (45 CFR 46.116(b)(5) (pre-2018 Common Rule) or 45 CFR 46.116(c)(5) (2018 Common Rule), and 21 CFR 50.25(b)(5) as applicable).

f. As a duly convened committee, the RCRC may exercise the full authority of an IRB including suspension or termination of IRB approval of research (see Policy 402 NIH IRB Meetings).

g. The office of Compliance and Training will report to appropriate regulatory authorities and institutional officials as described in Policy 801 Reporting Research Events.

h. An investigator may request reconsideration by the RCRC of a finding of serious and/or continuing non-compliance for good cause, such as submission of new information that was not considered or available during the investigation, material failure to follow the non-compliance policies, or that the corrective action(s) is perceived to exceed the severity of the non-compliance.

i. Requests for reconsideration will be submitted in writing to the Director of OHSRP for consideration, who has final authority to determine if the finding will be reconsidered by the RCRC.

6. When the NIH is relying on an external Reviewing IRB, any allegations of possible non- compliance received by the office of Compliance and Training that have not already been reported to the Reviewing IRB will be communicated to the Reviewing IRB based on that IRB's reporting requirements.
   a. The office of Compliance and Training will coordinate with the Reviewing IRB, with input from the OHSRP Director, the IRBO Director and/or the NIH Executive Chair, regarding any investigation of an allegation of non-compliance involving an NIH investigator.
   b. The Reviewing IRB has final regulatory authority to determine if the non- compliance is serious and/or continuing, unless otherwise specified in the terms of the reliance agreement.
   c. NIH will work with the Reviewing IRB in developing corrective action as needed to assist with resolution of the problem
   d. If the Reviewing IRB determines the non-compliance to be serious and/or continuing, the office of Compliance and Training will report to the appropriate NIH officials as required by Policy 801-Reporting Research Events.
   e. The policies of the Reviewing IRB will apply to the appeal of any determinations of serious and/or continuing non-compliance, unless otherwise specified by the terms of the reliance agreement.
7. The IC leadership or other institutional authorities, such as the Institutional Official, have the authority to take restrictive measures above and beyond what has been required by the Reviewing IRB including, stopping research activities, closure of the protocol, or other actions within the scope of its authority (see *Policy 102 NIH's Human Research Protection Program (HRPP)* and *Policy 103 Organizational Structure of the OHSRP*).
8. At the conclusion of the investigation, the office of Compliance and Training will notify the complainant consistent with federal law and policy.

F. References

1. Federal Regulations
   HHS: 45 CFR 46
   FDA: 21 CFR
2. NIH Policy

   Policy 102 NIH's Human Research Protection Program (HRPP) Policy 103 Organizational Structure of the OHSRP

   Policy 302 IRB Membership and Composition Policy 402 IRB Meetings;

   Policy 801 Reporting Research Events
3. Guidance: NA

G. Appendices: None

H. Revision History: NA

I. Supersedes Date: 07/01/2019

SOP 16A Allegations of Non-compliance with Requirements of the NIH Human Research Protection Program (HRPP), versions:

V. 3, dated 03-17-2016

V. 2, dated 10-01-2013

V.1, dated 6-11-2013