Supplemental Material

Clinical response to OPC/EC:

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 be 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 of 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(s) 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 summary of the symptom scores will be used as the severity score.

Clinical response to VVC

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

Clinical response to onychomycosis

The investigator will assess the signs and symptoms of onychomycosis. For clinical response, the target thumbnail or great toenail will be assessed for the presence, absence, or improvement of onychomycosis and subungual hyperkeratosis, and the percentage of nail involvement will be estimated and recorded. 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.

Endoscopic evaluations

Patients with a diagnosis of EC will undergo a clinically indicated upper endoscopic evaluation under either conscious sedation or general anesthesia within 4 weeks before

CAMB initiation. These patients will also undergo a second upper endoscopy for research purposes only at the 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

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 follows:

No growth

One colony

Scant growth

Light growth

Moderate growth

Heavy growth

Indeterminant growth: Extenuating circumstances preclude classification.

Measures of mycological response will include:

Eradication: No growth.

Partial response: Decrease in quantity of *Candida* from pre-treatment levels (e.g., 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.

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-parenteral antifungal treatment 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-parenteral treatment 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-parenteral treatment 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 entire 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 (e.g., 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 (e.g., 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, e.g., 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.

Patient exclusion criteria

Allergy to any AMB product or any component of CAMB (e.g., phosphatidylserine)

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.

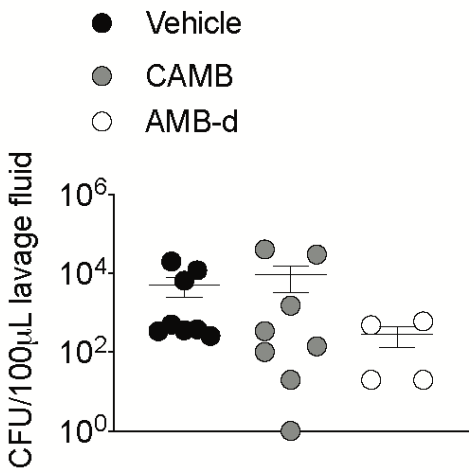

Figure S1. CAMB and AMB-d do not decrease fungal burden in the vaginal secretions in a mouse model of vulvovaginal candidiasis. *Act1*$^{-/-}$ mice were infected vaginally with *C. albicans*. Mice were treated daily with CAMB via oral gavage or AMB-d intraperitoneally starting at day 1 post-infection. At day 5 post-infection, the mice were euthanized, and vaginal secretions were harvested to quantify fungal burden. n = 4-8 per group; data are summary of two independent experiments. AMB, amphotericin B; CAMB, cochleated AMB; AMB-d, AMB-deoxycholate; VVC, vulvovaginal candidiasis.