

# **CLINICAL STUDY PROTOCOL**

## **A Multi-Center Randomized Study to Evaluate the Safety, Tolerability, and Efficacy of Oral Encochleated Amphotericin B (CAMB) Compared With Oral Fluconazole in the Treatment of Moderate to Severe Vulvovaginal Candidiasis**

**Investigational Product:** MAT2203 encochleated amphotericin B (CAMB)

**Protocol Number:** MB-70005

**IND Number:** 72,807

### **Sponsor:**

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**Amendment:** 3

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**Date:** 30 January 2017

### **Confidentiality Statement**

The information in this document is confidential and is not to be disclosed without the written consent of Matinas BioPharma Nanotechnologies, Inc. except to the extent that disclosure would be required by law and for the purpose of evaluating and/or conducting a clinical study for Matinas BioPharma Nanotechnologies, Inc. You are allowed to disclose the contents of this document only to your Institutional Review Board (IRB) and study personnel directly involved with conducting this protocol. Persons to whom the information is disclosed must be informed that the information is confidential and proprietary to Matinas BioPharma Nanotechnologies, Inc. and that it may not be further disclosed to third parties.

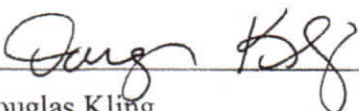
## SIGNATURE PAGE


**STUDY TITLE: A Multi-Center Randomized Study to Evaluate the Safety, Tolerability, and Efficacy of Oral Encocleated Amphotericin B (CAMB) Compared With Oral Fluconazole in the Treatment of Moderate to Severe Vulvovaginal Candidiasis**

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature

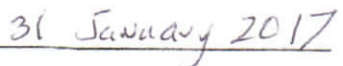
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J Carl Craft, MD  
Chief Medical Consultant/Chairman, Scientific Advisory Board  
Matinas BioPharma Nanotechnologies, Inc.

## INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Matinas BioPharma Nanotechnologies, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Matinas BioPharma Nanotechnologies, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Matinas BioPharma Nanotechnologies, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and ICH Guidelines for Good Clinical Practices.

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Investigator's Signature

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Date

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Investigator's Printed Name

## SYNOPSIS

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**TITLE:** A Multi-Center Randomized Study to Evaluate the Safety, Tolerability, and Efficacy of Oral Encochleated Amphotericin B (CAMB) Compared With Oral Fluconazole in the Treatment of Moderate to Severe Vulvovaginal Candidiasis

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**PROTOCOL NUMBER:** MB-70005

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**INVESTIGATIONAL PRODUCT:** MAT2203 encochleated amphotericin B (CAMB)

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**PHASE:** 2

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**INDICATION:** Moderate to severe vulvovaginal candidiasis

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### OBJECTIVES:

The primary objective of this study is to evaluate the safety of 200 mg (100 mg twice daily [BID]) and 400 mg (200 mg BID) doses of oral CAMB for 5 days compared with a single 150 mg dose of oral fluconazole in subjects with moderate to severe vulvovaginal candidiasis (VVC).

The secondary efficacy objectives of this study are the following:

- Assess the clinical cure rate of oral CAMB compared with oral fluconazole at the Test-of-Cure (TOC) Visit (Day 12);
- Assess the mycology eradication rate for oral CAMB compared with oral fluconazole at the TOC Visit (Day 12); and
- Assess the responder outcome by treatment group, separately, at the TOC Visit (Day 12).

The tertiary objective of this study is to assess optional pharmacokinetics (PK) (ie, area under the concentration-time curve [AUC], clearance [CL], maximum plasma concentration [ $C_{max}$ ], terminal elimination half-life [ $t_{1/2}$ ], and time to maximum plasma concentration [ $T_{max}$ ]) of CAMB after 5 days of oral administration.

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### POPULATION:

The population for this study will be women age 18 to 65 years, inclusive, with a clinical diagnosis of moderate to severe VVC.

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### STUDY DESIGN AND DURATION:

This is a proof-of-concept, multi-center, randomized study to evaluate the safety, tolerability, and efficacy of 200 mg (100 mg BID) CAMB and 400 mg (200 mg BID) CAMB compared with a single 150 mg dose of fluconazole in the treatment of moderate to severe VVC.

Approximately 100 women with moderate to severe VVC will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups (200 mg CAMB, 400 mg CAMB, or fluconazole). Randomization will be stratified by a signs and symptoms composite score of up to 12 (moderate) and  $\geq 13$  (severe).

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### Scoring of Symptoms and Signs of Vulvovaginal Candidiasis

Vulvovaginal candidiasis signs and symptoms will be evaluated at screening and Days 1, 5, and 12. Signs of VVC will be defined as the presence of erythema, edema, or excoriation. Symptoms of VVC will be defined as itching, burning, or irritation.

Each vulvovaginal sign and symptom will be objectively scored based on severity as follows:

- 0 = none (complete absence of any signs or symptoms),
- 1 = mild (slight),
- 2 = moderate (definitely present), or
- 3 = severe (marked, intense).

### Dosing Schedule

For subjects randomized to 200 mg CAMB and 400 mg CAMB, the preferred dosing regimen on Days 1 through 4 is 100 mg BID and 200 mg BID, respectively, with morning and evening meals. On Day 1, subjects will be administered the first dose according to their treatment assignment with a non-standardized meal or snack in the clinic.

On Day 1, subjects randomized to 200 mg CAMB who enroll in the afternoon can take both 100 mg doses as a single 200 mg dose or as 2 separate doses with a non-standardized meal or snack (once at enrollment and once in the evening); subjects randomized to 400 mg CAMB who enroll in the afternoon can take both 200 mg doses as a single 400 mg dose or as 2 separate doses with a non-standardized meal or snack (once at enrollment and once in the evening).

On Day 5, subjects randomized to 200 mg CAMB and 400 mg CAMB will be administered a single dose of 200 mg and 400 mg, respectively, in the clinic with a non-standardized meal or snack.

Other combinations of CAMB dosing are allowed throughout the study such that subjects randomized to 200 mg CAMB complete a course of ten 100 mg doses by Day 5 and subjects randomized to 400 mg CAMB complete ten 200 mg doses by Day 5. Subjects will be instructed to record their dosing in a patient diary.

Subjects randomized to fluconazole will take a single 150 mg tablet on Day 1 without respect to food.

### Visit Schedule

Participation in this study will consist of a screening period (up to 48 hours prior to Day 1); a 5-day treatment period (5 days with 200 mg or 400 mg CAMB or 1 day with fluconazole); a mandatory pre-dose PK assessment on Day 5 for determination of trough plasma concentrations of CAMB; an optional serial PK assessment for subjects who agree to participate; a TOC/Early Withdrawal Visit on Day 12 ( $\pm 2$  days), and a follow-up phone call between Days 21 to 30. For eligible subjects, screening and Day 1 can occur on the same day. Therefore, subjects who do not participate in the optional serial PK assessment will complete a total of 3 to 4 clinic visits, and subjects who do participate will complete a total of 4 to 5 clinic visits.

At screening, subjects must provide written informed consent prior to any study procedures being performed. Papanicolaou (Pap) smear/tests will be performed for subjects (>21 years of age) who do not have a negative test for intraepithelial lesion or malignancy or atypical squamous cells of

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undetermined significance in the past 36 months; in circumstances where the results of the Pap smear are pending at the time of randomization, eligible subjects may be randomized. Specimens will be collected for local testing to rule out *Trichomonas vaginalis*, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae*. Subjects may be enrolled pending test results. Subjects who are later confirmed to be positive for *C. trachomatis*, *N. gonorrhoeae*, or *T. vaginalis* will not be required to stop treatment and should be encouraged to complete all remaining study visits. Subjects will undergo a physical examination and speculum examination of the vagina. *Candida* infections will be identified locally prior to randomization by a positive potassium hydroxide (KOH) wet mount test from a vaginal smear revealing filamentous hyphae/pseudohyphae and/or budding yeast cells OR a vaginal culture identifying a *Candida* infection no more than 1 week prior to randomization; subsequently, *Candida* infections will be confirmed by vaginal culture at the central laboratory. Speciation and susceptibility testing will be performed on all positive fungal cultures. At the discretion of the Sponsor, sites may be instructed to send an additional specimen to the local laboratory for culture at baseline. Signs and symptoms of infection will also be assessed, including itching, burning, irritation, erythema, edema, and/or excoriation of the vagina and/or the vulva.

Safety assessments will include clinical laboratory assessments (including serum chemistry, hematology, and urinalysis), vital signs, body weight, electrocardiograms (ECGs), both complete and symptom-based physical examinations, prior and concomitant medication reporting, and adverse event reporting. Serum or urine pregnancy testing will be performed at screening and again at Day 1 if a subject's screening period exceeds 24 hours. Coagulation assessments and height will be performed at screening only.

On Day 1, subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized and begin dosing with 200 CAMB, 400 CAMB, or fluconazole. Before leaving the study facility on Day 1, subjects will be advised to contact the Investigator to be re-assessed at an office visit if symptoms do not improve within 2 to 3 days. Subjects will also be advised to contact the Investigator if other events occur that cause concern.

On Days 5 and 12, subjects will undergo a speculum examination of the vagina. Vaginal cultures will be sent to the central laboratory. *Candida* infections will be identified from vaginal cultures revealing filamentous hyphae/pseudohyphae and/or budding yeast cells identifying a *Candida* infection. Speciation and susceptibility testing will be repeated on all positive fungal cultures. Signs and symptoms of infection will also be assessed, including erythema, edema, excoriation, itching, burning, or irritation of the vagina and/or the vulva.

On Day 5 ( $\pm 1$  day for subjects not participating in the optional serial PK assessment), mandatory pre-dose PK blood samples will be collected from all subjects for determination of trough plasma concentrations of CAMB.

The optional serial PK assessment will include approximately 24 subjects randomized to 200 mg or 400 mg CAMB, with approximately 12 subjects in each group. For subjects who consent to participate in the optional serial PK assessment, additional blood samples will be collected on Day 5 at 1, 2, 3, 4, 8, and 12 hours, and 24 hours post-dose. In circumstances where the 12-hour PK assessment is not feasible, it will not be required. On Day 5, subjects randomized to 200 mg CAMB and 400 mg CAMB will be administered a single dose of 200 mg and 400 mg, respectively, in the clinic with a non-standardized meal or snack regardless of participation in the optional serial PK assessment.

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A follow-up phone call will occur between Days 21 to 30. Adverse events will be assessed.

### **Inclusion Criteria**

A subject will be eligible for participation in the study if all of the following criteria are met:

1. Must provide written informed consent and authorize disclosure of protected health information before any study-specific evaluation is performed;
2. Is female age 18 to 65 years, inclusive;
3. Has documented or suspected clinical diagnosis of moderate to severe VVC, defined as having a positive 10% KOH or saline preparation from the inflamed vaginal mucosa or secretions revealing yeast forms (hyphae or pseudohyphae) or budding yeasts;
4. Has 2 or more of the following signs and symptoms characterized as moderate in severity: itching, burning, irritation, erythema, edema, and/or excoriation of the vagina/vulva;
5. For women >21 years of age, documented Pap smear/test at baseline or during the previous 36 months reported as either “negative for intraepithelial lesion or malignancy” or “atypical squamous cells of undetermined significance;” Verbal documentation of the Pap smear results will be acceptable for this study; in circumstances where the results of the Pap smear are pending at the time of randomization, eligible subjects may be randomized;
6. Women of childbearing potential must have negative pregnancy test before randomization and may not be lactating or planning to become pregnant during the study period. A woman is considered of childbearing potential if she is not surgically sterile or if her last menstrual period was <12 months prior to screening;
7. Agreement of female subject of childbearing potential to use highly effective methods of contraception or to abstain from sexual intercourse. Acceptable methods of contraception for this study include use of intrauterine device or abstinence; all oral, transdermal, and hormonal contraceptives or selective estrogen receptor modulator contraceptives are acceptable as long as the dose and type have been stable for 3 months prior to screening;
8. Willing to refrain from the use of intravaginal products during the treatment period (eg, douches, spermicides, condoms, tampons, and diaphragms); and
9. Has vaginal pH  $\leq 4.5$  at screening.

### **Exclusion Criteria**

A subject will be excluded from participation in the study if any of the following criteria are met:

1. Has an intolerance or hypersensitivity to any amphotericin B (AMB) product, any component of CAMB (eg, phosphatidylserine), or to azole antifungal drugs (eg, fluconazole, itraconazole, voriconazole, isavuconazole, and posaconazole);
2. Is currently receiving antifungal therapy unrelated to VVC or has evidence of systemic fungal infections requiring antifungal therapy;
3. Has received treatment for VVC within the past 30 days or has experienced 4 or more episodes of VVC diagnosed by a physician after clinical evaluation in the past 12 months, of which 2 of the 4 episodes were confirmed by positive *Candida* culture; subjects who only have self-reported episodes of VVC in the past may still be considered for participation;

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4. Has another cause or suspected cause of vulvovaginitis (eg, *T. vaginalis*, bacterial vaginosis, genital herpes);
  5. Has an active human papillomavirus infection;
  6. Has other urogenital infection(s) that would potentially alter their response to disease;
  7. Has confirmed or suspected *N. gonorrhoea* or *C. trachomatis*;
  8. Has another vaginal or vulvar condition that would confound the interpretation of clinical response;
  9. Has a physiological or pathological condition that would confound the interpretation of clinical response (eg, cervicitis, aerobic vaginitis, atrophic vaginitis, and mucoid ectopy);
  10. Has any of the following laboratory abnormalities at screening:
    - a. Alanine aminotransferase (ALT), or aspartate aminotransferase, or alkaline phosphatase levels  $>5 \times$  upper limit of normal (ULN);
    - b. Total bilirubin level  $>2.5 \times$  ULN;
    - c. Estimated creatinine clearance  $<70$  mL/min;
    - d. Absolute neutrophil count less than 500 cells/ $\mu$ L; or
    - e. Potassium level  $\leq 3.5$  mmol/L;
  11. Plans to undergo treatment or surgery for cervical intraepithelial neoplasia or cervical carcinoma during the study period;
  12. Has any known azole-resistant *Candida* infection;
  13. Has documented Type I diabetes mellitus, use of insulin, or glycosylated hemoglobin A<sub>1c</sub> level  $>10\%$  within 6 months of enrollment;
  14. Has previously diagnosed human immunodeficiency virus seropositivity or clinically diagnosed acquired immunodeficiency syndrome or its related complex;
  15. Has a known immunosuppressive condition (eg, end-stage renal disease) or is currently taking immunosuppressants, (eg, steroids, cyclosporine);
  16. Is currently receiving therapy with a drug known to prolong QTc interval that is metabolized via the cytochrome P450 3A4 enzyme, such as cisapride, astemizole, pimozone, and quinidine;
  17. Has been exposed to any investigational agent during the last month (30 days or 5 half-lives, whichever is longer) prior to screening; or
  18. Has any other condition the Investigator believes would interfere with the subject's ability to provide informed consent, comply with study instructions, or puts the subject at undue risk.
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#### **DOSAGE FORMS AND ROUTE OF ADMINISTRATION:**

Enochleated amphotericin B will be administered as a 5 mg/mL oral suspension of 200 mg (100 mg [20 mL] BID) or 400 mg (200 mg [40 mL] BID) amphotericin B on Days 1 through 5.

Fluconazole will be administered once as a single 150 mg tablet on Day 1.

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### **ANALYSIS POPULATIONS:**

The Intent-to-Treat Population (ITT) will include all subjects who were randomized.

The Modified Intent-to-Treat (mITT) Population will include all randomized subjects who have a *Candida* species isolated on culture of vaginal specimen at baseline based on the central laboratory results.

The Safety Population will include all ITT subjects who received at least 1 dose of study drug.

The PK Population will include the subjects in the ITT Population with at least 1 PK sample.

The Per-Protocol Population will include all of the mITT subjects who meet the following criteria:

- No key inclusion/exclusion violations;
- Received the complete course of study drug;
- No major protocol violations that would affect the treatment evaluation; and
- Has not received another systemic or topical antifungal drug that has documented activity against the causative organism before the TOC assessment, unless the subject has a therapeutic response of failure at a previous assessment visit.

### **EFFICACY VARIABLES:**

The efficacy endpoints for this study will be performed on the mITT Population and Per-Protocol Population and will include the following:

1. The proportion of subjects with clinical cure at the TOC Visit (Day 12);
2. The proportion of subjects with mycological eradication at the TOC Visit (Day 12); and
3. The proportion of subjects with overall success at the TOC Visit (Day 12).

For the definition of clinical cure, mycological eradication, and overall success, see below.

#### Assessment of Clinical Outcome

Clinical outcomes will be assessed at the TOC Visit (Day 12) according to the following definitions:

- Clinical cure – resolution of the VVC signs and symptoms that were present at baseline without further antifungal treatment. Specifically, any sign or symptom with a score of 1 or 2 at entry should be absent (score = 0) by the TOC Visit. Any sign or symptom with a score of 3 (severe) at entry should have a score of 0 or 1 by the TOC Visit. If a new sign or symptom is observed at the TOC Visit that was not present at entry, the Investigator should state whether the new sign or symptom is related to VVC or not (ie, if related, the subject would be considered a failure; if not related, the subject may be considered a cure);
- Clinical failure – incomplete resolution of signs and symptoms of VVC that were present at baseline or new signs and symptoms have developed and require the initiation of non-study antifungal drugs; and
- Clinical indeterminate – insufficient data are available to determine if the subject is a cure or failure.

### Assessment of Mycological Outcome

Mycological outcomes will be assessed at Day 12 ( $\pm 2$  days) (TOC Visit) according to the following definitions:

- Mycological eradication – a vaginal swab culture negative for growth of baseline *Candida* species;
- Mycological persistence – a vaginal swab culture positive for growth of baseline *Candida* species; and
- Mycological indeterminate – no vaginal swab culture is available, or the culture cannot be interpreted for any reason, or the culture is considered contaminated.

### Assessment of Overall Response

Overall response will be assessed at Day 12 ( $\pm 2$  days) (TOC Visit) according to the following definitions:

- Overall success – achievement of both a clinical cure AND microbiologic eradication;
- Overall failure – clinical failure OR microbiological persistence; and
- Overall indeterminate – insufficient data are available to determine if the subject is an overall success or failure.

The assessment of overall response at the TOC Visit is summarized below.

### **Summary of Overall Response at the Test-of-Cure Visit**

Clinical Outcome	Mycological Outcome		
	Eradication	Persistence	Indeterminate
Cure	Success	Failure	Indeterminate
Failure	Failure	Failure	Failure
Indeterminate	Indeterminate	Failure	Indeterminate

### **SAFETY VARIABLES:**

Safety assessments will include clinical laboratory assessments (including serum chemistry, hematology, and urinalysis), vital signs, body weight, ECGs, both complete and symptom-based physical examinations, prior and concomitant medication reporting, and adverse event reporting.

#### Hepatotoxicity

Hepatotoxicity will be defined as post-baseline aminotransferase  $\geq 3 \times$  ULN.

#### Nephrotoxicity

Nephrotoxicity will be defined as a 50% increase in serum creatinine from baseline or an increase by  $\geq 0.3$  mg/dL.

#### Hypokalemia

Hypokalemia will be defined as serum potassium  $\leq 2.5$  mmol/L.

### **PHARMACOKINETIC PARAMETERS:**

The PK parameters will include the following:

- AUC: area under the concentration-time curve,
  - CL: clearance,
  - C<sub>max</sub>: maximum plasma concentration,
  - C<sub>trough</sub>: concentration of pre-dose CAMB,
  - t<sub>1/2</sub>: terminal elimination half-life, and
  - T<sub>max</sub>: time to maximum plasma concentration.
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### **STATISTICAL ANALYSES:**

Summary statistics will be presented by treatment group. For continuous variables, the number of observations (n), mean, standard deviation, median, minimum, and maximum will be provided. For categorical variables, the frequency and percentage in each category will be displayed.

Efficacy analyses will be performed on the mITT and Per-Protocol Populations. The percentage of subjects with clinical cure, mycological eradication, and overall success will be summarized descriptively by treatment group. Clinical outcome, mycological outcome, and overall response will also be tabulated by treatment group.

Safety analyses will be performed on all subjects in the Safety Population. Analyses will be based on adverse events, vital signs, clinical laboratory assessments, physical examination findings, and ECGs. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

The proportion subjects with hepatotoxicity, nephrotoxicity, and hypokalemia will be summarized by treatment group

Descriptive statistics will be provided for PK concentration data and PK parameters. All PK analyses will be performed using the PK Population.

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### **SAMPLE SIZE DETERMINATION:**

Approximately 75 subjects are planned for the mITT population. Assuming 75% of randomized subjects will be evaluable for the mITT Population, a total of approximately 100 subjects will be randomized. The sample size was determined empirically rather than with a specific statistical rationale and is considered sufficient to achieve the study objectives. No formal sample size calculations were made.

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**SITES:** Approximately 20 sites in the United States.

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**SPONSOR:**

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