SCYNEXIS, Inc.

Clinical Trial Protocol

An Open-Label Pharmacokinetic Study in Healthy Lactating Women after Two Oral Doses of Ibrexafungerp Administered on a Single Day

SCYNEXIS Protocol Number SCY-078-121

SCYNEXIS, Inc.

1 Evertrust Plaza, 13th Floor
Jersey City, NJ 07302

Protocol Version 1.0:	11-July-2022
Protocol Version 2.0 (Amendment 01)	04-October-2022
Protocol Version 3.0 (Amendment 02)	26-May-2023
Protocol Version 4.0 (Amendment 03)	13-March-2024

US IND Number 107,521

1.1. Version 4.0 Summary of Changes (13-March-2024):

Change Made	Location in Protocol
Sponsor contact information updated	Section 2.0 Contact Information, Section 3.0 Protocol Approvals
Interim analysis related text added	Synopsis, Section 7.2.2 Rationale for Interim Analysis, Section 9.1 Overall Study Design, Section 9.2 Number of Participants, Section 10.2 Participant Withdrawal Criteria, Section 15.2 Sample Size Determination, and Section 15.5 Interim Analysis
Footnote "f" was revised to remove "serum" from the alcohol screening text. The site's standard for alcohol screening will be utilized. An "X" was added to the Day 5 (Post-Study) weight measurements assessment to align with the corresponding text in Section 11.7.5 (Day 5 (Post-Study))	Table 5 Schedule of Assessments
Reference to the site's smoking policy removed	Section 11.3.3 Smoking Restrictions
The caloric intake of standard meals was increased to accommodate the needs of lactating women (average of ~300 extra calories per day).	Section 11.5.1 Standard Meal
The prestudy screening window has been modified from 2 weeks to 4 weeks, which aligns with the Duration of Treatment text (Synopsis and Section 9.1 (Overall Study Design)) of 4 to 5 weeks.	Section 11.7.1 Prestudy Screening ~~Day -14~~ **Day -28** to Day -1, Table 5 Schedule of Assessments (Footnote "a")
The predose safety labs and serum pregnancy test window was modified from 24 hours predose to 24**-48** hours predose.	Section 11.7.2 (Predose (Prior to Day 1 Morning Dosing)
Last sentence was removed to clarify that all study medication will be dispensed while participants are domiciled.	Section 12.1 Study Drug
The calculation for M/P has been added.	Synopsis, Section 15.4 Pharmacokinetic Analysis

1.2. Version 3.0 Summary of Changes (26-May-2023):

Change Made	Location in Protocol
Clinical site information removed. Project Manager information updated. CRO project manager information combined.	Section 2.0 Contact Information
Site information removed and placeholders added	Synopsis and Investigator's Agreement Statement
Study center(s) field updated to "One (1) to 2 sites", Country field updated, and Study period (years) field dates updated	Synopsis
Inclusion criterion #4 updated for consistency purposes and to include "acceptance of bottle feeding". Inclusion criterion #9 updated to include vaping.	Section 10.1.1 Inclusion Criteria
Herbal products allowed to increase breast milk production updated.	Section 11.2 Prior and Concomitant Medications
Added text indicating acceptance of bottle feeding prior to study start. Added text related to breast feeding restrictions if a participant discontinues early.	Section 11.3.5 Breast Feeding
"Clinical research unit" text added and SAE reporting window clarified to align with Appendix B text.	Section 14.2.9 Reporting Adverse Events

1.3. Version 2.0 Summary of Changes (04-October-2022):

Change Made	Location in Protocol
Added text related to the benefits of breastfeeding compared to the risks of interruption of breastfeeding, including the potential for changes in milk supply and difficulty re-establishing breastfeeding after the study is completed.	Section 7.2.1 Benefits and Risks of Breastfeeding and Section 9.4.1 Potential Risks
Clarified the window prior and concomitant medication is 14 days prior to dosing (Day 1) and throughout the poststudy.	Section 11.2 Prior and Concomitant Medications and Section 14.1.6.9 Adverse Event and Concomitant Medication Assessment
Updated pre-dose safety lab and serum pregnancy sampling window extension to **24hrs predose** instead of 12hrs predose.	Table 5 Schedule of Assessments and Section 11.7.2 Predose (Prior to Day 1 Morning Dose)
Added "serum pregnancy to have a sensitivity of at least 25 mIU/L."	Section 14.1.6.7 Pregnancy Screen
Clarified the window for AEs and concomitant medications should be collected only **through post study**.	Section 14.1.6.9 Adverse Event and Concomitant Medication Assessments Section 14.2.8 Recording Adverse Events
Clarified serious adverse event information will be collected from time of informed through **the poststudy visit**.	Section 14.2.8 Recording Adverse Events
Clarified the vital signs <0 hours timepoint (pre-dose) acceptable time window may be performed up to **12 hours predose.**	Appendix A: Time Window for Serial Assessments

2. CONTACT INFORMATION

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Sponsor Project Manager	

3. PROTOCOL APPROVALS

Sponsor's Approval Signature Page

PROTOCOL ID: SCY-078-121

An Open-Label Pharmacokinetic Study in Healthy Lactating Women after Two Oral Doses of Ibrexafungerp Administered on a Single Day

The protocol has been approved by SCYNEXIS, Inc.

Sponsor's Authorized Officer:

Michelle Middle, MD Medical Director, Clinical Development SCYNEXIS, Inc. 1 Evertrust Plaza, 13th Floor Jersey City, NJ 07302 Phone: +27.82.4934.621 Email: michelle.middle@scynexis.com	Date

Investigator's Agreement Statement

PROTOCOL ID: SCY-078-121

An Open-Label Pharmacokinetic Study in Healthy Lactating Women after Two Oral Doses of Ibrexafungerp Administered on a Single Day

I understand that all documentation provided to me by SCYNEXIS, Inc. or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, Investigator's Brochure, case report forms, and other scientific data. This study will not commence without the prior written approval of a properly constituted Institutional Review Board or Ethics Committee. No changes will be made to the study protocol without the prior written approval of SCYNEXIS, Inc. and the Institutional Review Board/Ethics Committee, except where necessary to eliminate an immediate hazard to the participant. All participants will provide a written informed consent prior to participation.

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol, and in compliance with International Conference on Harmonization (ICH) guidelines, Good Clinical Practices (GCP), Safety Reporting obligations and any applicable local requirements.

_____ _____

Principal Investigator's Signature Date

_____

Print Principal Investigator's Name

Principal Investigator

_____
Site Name

_____

_____
Site Address

4. SYNOPSIS

Name of Sponsor/Company:
SCYNEXIS, Inc.

Name of Investigational Product:
Ibrexafungerp

Name of Active Ingredient:
Ibrexafungerp

Protocol Number: SCY-078-121	**Phase:** 1	**Country:** US

Title of Study:
An Open-Label Pharmacokinetic Study in Healthy Lactating Women after Two Oral Doses of Ibrexafungerp Administered on a Single Day

Study center(s): One (1) to 2 sites

Studied period (years):
Estimated date first patient enrolled: July 2023
Estimated date last patient completed: July 2024

Objectives:

Primary Objective:

- To determine whether ibrexafungerp is excreted in breast milk and if so, to characterize ibrexafungerp pharmacokinetics (PK) in the breast milk and plasma of lactating women.

Secondary Objectives:

- To calculate the potential infant exposure to ibrexafungerp if lactating women are treated with ibrexafungerp.
- To characterize the safety and tolerability of ibrexafungerp in lactating women.

Study Design:
Ibrexafungerp is approved in the United States as a single day, two-dose therapy for women with vulvovaginal candidiasis (VVC). This is a Phase 1 study designed to determine whether this dose of ibrexafungerp is excreted in breast milk, and if so, to characterize ibrexafungerp PK in the breast milk and plasma of lactating women.

Participants will receive a single day of twice daily (BID) 300-mg (2 x 150-mg) oral ibrexafungerp doses given 12 hours apart (Q12H). Participants will receive both doses on site. Participants will be admitted to the clinic on Day -1, and may be discharged on Day 5, after the 108-hour procedures are completed, at the discretion of the Investigator.

Product, Dose, and Timing	Study Day
Ibrexafungerp 300-mg BID on Day 1	1

Safety will be monitored with laboratory and clinical evaluations: vital signs, physical examinations, and the collection of adverse events (AE) and concomitant medications. Breast milk and plasma PK

samples will be obtained at selected intervals and time points pre-dose and post-dose for determination of ibrexafungerp concentrations.

An interim analysis will be performed after 5 subjects have completed the study.

Number of participants (planned):

Up to 10 healthy lactating females who are at least 10 days postpartum with a fully established milk supply and are between the ages of 18 and 50 years at the time of screening. Participants who discontinue or are discontinued may be replaced to ensure that an adequate number of participants to achieve the study objectives, complete the study.

Investigational Product, Dosage, and Mode of Administration:

The study drug, ibrexafungerp citrate salt tablets, will be provided as oral 150-mg tablets, by the Sponsor.

All participants will receive ibrexafungerp in two 300-mg (2 x150-mg tablets) oral doses given Q12H with food.

Ibrexafungerp citrate salt tablets will be stored at room temperature in a secure and locked location in the clinical research unit.

Duration of Treatment:

The duration of study participation from pre-study through post-study safety monitoring will be approximately 4 to 5 weeks for participants.

Criteria for evaluation:

Pharmacokinetics:

Breast milk will be obtained up to 108 hours post dose and blood samples will be obtained starting pre-dose the Day 1 morning dose until 108 hours post first dose of study drug for determination of ibrexafungerp concentrations. Sample time points are as follows:

- Breast Milk: **complete expression** of milk from both breasts (using a standard electric breast pump) will be obtained at the following timepoints and intervals: pre-dose, 0-2, 2-4, 4-8, 8-12, 12-18, 18-24, 24-36, 36-48, 48-72, and 72-108 hours post first dose of study drug.
- Plasma samples will be obtained at the following timepoints: 0 hours (prior to first dose), and at 2, 6, 8, 12 (prior to second dose), 24, 36, 48, 72, and 108 hours post first dose of study drug for determination of ibrexafungerp in plasma concentrations. The 12-hour samples will be taken prior to the second dose of ibrexafungerp.

The following plasma pharmacokinetic parameters: area under the curve (AUC), peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), plasma clearance or apparent oral clearance (CL/F), apparent volume of distribution (V_d), and terminal half-life ($t_{1/2}$) for ibrexafungerp following oral administration of the VVC dosage regimen for ibrexafungerp will be determined for both breast milk and plasma concentrations.

The daily infant dosage (total drug present in milk and consumed by the infant per day) will be calculated:

- *Daily Infant Dosage (mg/day) = Σ (total drug concentration in each milk collection multiplied by the expressed milk volume in each milk collection)*

The Milk Plasma ratio (M/P) will be calculated. M/P = AUC_{0-24} milk/AUC_{0-24} plasma.

The calculation of M/P should be based on AUC and on multiple time points over 24 hours and not just a single point in time.

The relative infant dose (the percent of the weight-adjusted maternal dosage consumed in breast milk over 24 hours) will be calculated:

- *Relative Infant Dose = Infant Dosage (mg/kg/day)/Maternal Dosage (mg/kg/day) multiplied by 100*

The PK of ibrexafungerp plasma and breastmilk will be assayed using validated LC-MSMS methods.

Safety:

Safety and tolerability will be assessed during the study by the collection of adverse events, vital signs (blood pressure, heart rate, respiratory rate, and temperature), physical examinations, and clinical laboratory assessments (including biochemistry, hematology, coagulation, and urinalysis). For each participant, adverse events will be monitored from the time of consent through poststudy visit.

Statistical Methods:

Pharmacokinetics:

Individual participant plasma and breast milk concentrations, actual milk and blood sampling times, actual volume of milk collected per interval, actual dosing information (actual time and date of dosing, and actual dose taken), and PK parameters for individuals and the group will be listed in tabular format. Plasma ibrexafungerp concentrations measured over time will be displayed graphically. Plasma ibrexafungerp concentrations and PK parameters will be summarized using descriptive statistics. The PK parameters of ibrexafungerp will include AUC, C_{max}, T_{max}, CL/F, V_d, and $t_{1/2}$.

Breast milk concentrations and PK parameters will be summarized using descriptive statistics. For the PK parameters of ibrexafungerp in breastmilk: AUC for the different collection periods, C_{av} based on AUC derived from collections at different time points; total milk concentration data will be used to calculated C_{max}, C_{min} and T_{max}.

Interim Analysis:

An interim analysis will be conducted after five subjects have completed their participation in the study. The analysis will involve the examination of pharmacokinetic and safety data and will comprise a full analysis as described in the SAP. The objective of the interim analysis is to determine whether the data from 5 participants is sufficient to address the objectives of the study and fulfill the post marketing requirement (PMR 4069-2); if not the study shall continue to recruit up to 10 participants.

The reporting analysis will involve descriptive statistical methods, including summaries, tabulations, graphs, or by-subject listings. Before initiating this analysis, the data for the study endpoints will undergo a thorough cleaning process, and the database will be soft-locked.

Safety:

All adverse events and other safety evaluations (vital signs and clinical safety laboratory tests) will be listed by participant and tabulated. Summary statistics and plots for safety parameters will be generated for the change from baseline values, as deemed clinically appropriate. Adverse events will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) and presented by system organ class and preferred terms.

Statistical Power:

There is no formal power calculation. The N is based on practical aspects of recruitment in this population. A sample size of up to 10 participants to complete the study is selected, with the intention of stopping the study at the interim analysis if the data from 5 participants are considered to be adequate to meet study objectives.

5. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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6. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALT	Alanine Aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 to infinity
BID	Twice a day
BMI	Body Mass Index
BP	Blood pressure
°C	Degrees Celsius
CFU	Colony forming unit
CI	Confidence interval(s)
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent total clearance of the drug from plasma after oral administration
C_{max}	Maximum concentration
CPK	Creatine phosphokinase
CRO	Contract Research Organization
CT	Compressed tablet
CYP3A4	Cytochrome P450 3A4
DFC	Dry filled capsule
ECG	Electrocardiogram
ECI	Event of clinical interest
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HCT	Hematocrit
HgB	Hemoglobin
HR	Heart rate

Abbreviation or Specialist Term	Explanation
H or hr	Hour
β-hCG	Human Chorionic Gonadotropin
Σ	Total drug concentration in each milk collection multiplied by the expressed milk volume in each milk collection
IB	Investigator's Brochure
IC	Inhibitory concentration
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IPA	Invasive pulmonary aspergillosis
IRB/EC	Institutional Review Board/Ethics Committee
Kcal	Kilocalories
kg	Kilograms
KOH	Potassium Hydroxide
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
M/P	Milk plasma ratio
OAE	Other Adverse Event
OCP	Oral contraceptive pills
OTC	Over-the-counter
PI	Principal Investigator
PK	Pharmacokinetics
PMR	Post Marketing Requirement
PT	Prothrombin time
Q12H	Every 12 hours
RBC	Red blood cell
REB	Research Ethics Board
RR	Respiratory rate
rVVC	Recurrent vulvovaginal candidiasis
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	Standard of Care; System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected, Unexpected Serious Adverse Reaction
T	Temperature

Abbreviation or Specialist Term	Explanation
$t_{½}$	Terminal half-life
TEAE	Treatment Emergent Adverse Event
TG	Triglycerides
TLF	Tables, Listings, and Figures
T_{max}	Time to maximum concentration
WBC	White blood cell
V_d	Apparent volume of distribution
VVC	Vulvovaginal candidiasis

7. INTRODUCTION

7.1. Background

Vulvovaginal Candidiasis

Vulvovaginal candidiasis (VVC) is a common fungal infection caused by *Candida* spp. and is a significant morbidity condition in women from all social classes.

Information on the incidence of VVC is incomplete, since the disease is not a reportable entity and data collection is hampered by inaccuracies of diagnosis and the use of non-representative study populations (Sobel, 2007). VVC affects 70%–75% of women at least once during their lives, most frequently young women of childbearing age. Approximately 40%–50% of women will experience a recurrence (Hurley and De Louvois, 1979) and 5% to 8% of adult women have a recurrent vulvovaginal candidiasis (Foxman et al, 1998).

Current treatments for VVC include topical antifungals and the use of prescription oral antifungals such a single dose of fluconazole. In two vaginal candidiasis studies conducted with fluconazole, the therapeutic cure rate, defined as the resolution of signs and symptoms of vaginal candidiasis along with negative potassium hydroxide (KOH) examination and negative culture for *Candida*, was achieved by 55% of participants receiving single doses of fluconazole 150 mg. The therapeutic cure rate is reduced to 40% in participants with a history of recurrent vaginitis (Pfizer, 2014 and Sobel, 2006). Although a single dose of fluconazole is able to provide an acceptable therapeutic outcome for more than half of the treated individuals, the emergence of fluconazole resistance among *C. albicans* isolates and the frequency of cases caused by *C. glabrata*, a strain naturally less susceptible to fluconazole, signals the need for new therapeutic approaches.

Additionally, recurrence of VVC after fluconazole therapy is not uncommon and these exacerbations often involve the same microorganism identified in the initial episode, suggesting that a small number of *C. albicans* remain as a reservoir in the vagina after completion of azole therapy, becoming the source of subsequent exacerbations. This may be explained by the fact that azoles are fungistatic, which means that they slow the growth of, but do not kill, the fungus and azoles are not active against certain species of *Candida* that cause VVC.

New curative approaches are needed, particularly involving agents with fungicidal activity (ie, that are able to kill the fungus) and activity against fluconazole-resistant strains, so that the causative yeasts can be eradicated. A new therapeutic approach with these characteristics would be expected to result in improved short-term and potentially long-term outcomes for this condition.

Ibrexafungerp is the first of the triterpenoid class of ß-1,3-D glucan synthase inhibitors. It is a semi-synthetic derivative of the natural product enfumafungin with in vitro and in vivo activity against *Candida species*.

It has the same molecular target as the echinocandins but is structurally distinct and may interact differently at the target due to its activity against echinocandin-resistant strains.

Ibrexafungerp has fungicidal in vitro activity against Candida species similar to that observed with the echinocandins. By way of comparison, the azoles are fungistatic, with colony forming unit (CFU) counts that parallel the growth control arm.

In June 2021 the US Food and Drug Administration (FDA) approved Ibrexafungerp (Brexafemme Label, 2021) for treatment of Vulvovaginal candidiasis.

Adult Pharmacokinetics Summary: After oral, single-dose administration, peak plasma ibrexafungerp concentrations occur within approximately 4 to 6 hours post-dose. Plasma concentrations declined from C_{max} in an approximately monophasic decline, with a harmonic mean terminal half-life ($t_{½}$) of ~20 hours. The mean $AUC_{0-\infty}$ and C_{max} appeared, in general, to be dose proportional for doses from 10 mg to 1600 mg. Plasma exposures of ibrexafungerp were not altered in participants who were older than 65 years compared to younger participants or in female compared to male participants after single oral dose administration.

Ibrexafungerp elimination is primarily hepatic metabolism; and approximately 1 to 2% of the total dose is excreted by the kidney following administration of a single IV dose.

Approximately 1625 participants received at least one dose of ibrexafungerp in completed and ongoing clinical studies: Phase 1 studies in healthy participants (n=468), in patients with liver impairment (n=16) and in patients with vulvovaginal candidiasis (VVC) (n=16) and Phase 2 and 3 studies (n=1125) in patients with either invasive / severe mucocutaneous fungal infections or VVC. Ongoing clinical studies include one Phase 1 study evaluating IV liposomal formulation of ibrexafungerp in healthy participants, one Phase 1 study in healthy participants and VVC patients, one Phase 2 study in patients with invasive pulmonary aspergillosis (IPA), one Phase 3 study in patients with fungal diseases refractory or intolerant to standard-of-care (SOC) treatment, and one Phase 3 study in patients with documented *C. auris* infection.

Ibrexafungerp was generally well tolerated following single oral doses of up to 1600 mg and multiple oral doses of up to 800 mg for 28 consecutive days administered as dry filled capsules (DFCs), phosphate compressed tablets (CTs) or citrate CTs in Phase 1 studies.

Most of the adverse events (AEs) considered related to oral ibrexafungerp across studies were of gastrointestinal (GI) nature and included, but were not limited to, diarrhea, abdominal pain, nausea, and vomiting. Headache was also a frequently reported treatment-related AE with oral dosing. Most treatment-related AEs reported with oral ibrexafungerp were mild to moderate in severity. Despite gastric mucosal degeneration findings in rat and dog studies, serum gastrin levels and gastric biopsies have not shown clinically significant gastrin level changes or histological evidence of mucosal degeneration in healthy volunteers.

Refer to the Investigator's Brochure (IB) and the Brexafemme® (ibrexafungerp) label (Brexafemme Label, 2021) for additional information.

7.2. Rationale for Trial

The primary purpose of this study is to determine whether ibrexafungerp is excreted in breast milk of lactating women, and if so, to characterize PK in breast milk and plasma; calculate the potential infant exposure if lactating women are treated with ibrexafungerp; and characterize the safety and tolerability in lactating women. Based on 24-hour half-life, it is expected that approximately 15% of ibrexafungerp remains after 72 hours, so the collection period of 0 through 108 hours is considered sufficient to characterize the PK parameters.

Vulvovaginal candidiasis (VVC) is a common genital infection in women caused by *Candida spp*., primarily *C. albicans* and *C. glabrata*. Several studies have reported that 75% of

women experience at least one episode of VVC during their lifetime and 5 to 10% experience recurrent VVC (rVVC) (Sobel, 2007).

Based on FDA Lactation Study Guidance (FDA Guidance, 2019), this drug has expected use in women of reproductive age similar to the marketed drugs that are currently commonly used for the indication of VVC in reproductive aged women.

Consequently, evaluation of products for treatment of lactating women with VVC is of importance.

7.2.1. Benefits and Risks of Breastfeeding

The benefits of breastfeeding compared to the risks of interruption of breastfeeding, including the potential for changes in milk supply and difficulty re-establishing breastfeeding after the study will be discussed with the participants.

7.2.2. Rationale for Interim Analysis

Given the nature of the study population and practical aspects of conducting a study in lactating women, a decision was taken to include an interim analysis to determine whether the data from 5 participants is sufficient to address the objectives of the study and fulfill the post marketing requirement (PMR 4069-2); if not the study shall continue to recruit up to 10 participants.

An interim study analysis with full analysis of the PK as described in Section 15.5, and safety data collected from these first 5 subjects will be carried out.

The reporting analysis will involve descriptive statistical methods, including summaries, tabulations, graphs, or by-subject listings. Before initiating this analysis, the data for the study endpoints will undergo a thorough cleaning process, and the database will be soft-locked.

8. TRIAL OBJECTIVES AND PURPOSE

8.1. Primary Objective

- To determine whether ibrexafungerp is excreted in breast milk and if so, to characterize ibrexafungerp pharmacokinetics (PK) in the breast milk and plasma of lactating women.

8.2. Secondary Objectives

- To calculate the potential infant exposure to ibrexafungerp if lactating women are treated with ibrexafungerp.
- To characterize the safety and tolerability of ibrexafungerp in lactating women.

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design

Ibrexafungerp is approved in the United States as a single day, two-dose therapy for women with vulvovaginal candidiasis. This is a Phase 1study designed to determine whether this dose of ibrexafungerp is excreted in breast milk, and if so, to characterize ibrexafungerp PK in the breast milk and plasma of lactating women. Up to 10 healthy lactating females who are at least 10 days postpartum with a full milk supply established and are between the ages of 18 and 50 years at the time of screening are planned to be enrolled. (Enough participants will be enrolled to complete up to 10 evaluable participants.)

Participants will receive a single day of twice daily (BID) dosing given 12 hours apart (Q12H) oral 300-mg ibrexafungerp. Participants will receive both doses on site.

Participants will be admitted to the clinic prior to dosing on Day -1, and may be discharged on Day 5, after the 108-hour procedures are completed, at the discretion of the investigator. The duration of study participation from pre-study through post-study safety monitoring will be approximately 4 to 5 weeks for participants.

Safety will be monitored with clinical and laboratory evaluations. Breast milk and plasma samples will be obtained at selected time points pre-dose and post-dose for determination of ibrexafungerp concentrations.

Participants who discontinue or are discontinued may be replaced at the discretion of the investigator and Sponsor to ensure that up to 10 evaluable participants complete the study. An interim analysis will be performed after 5 subjects have completed the study.

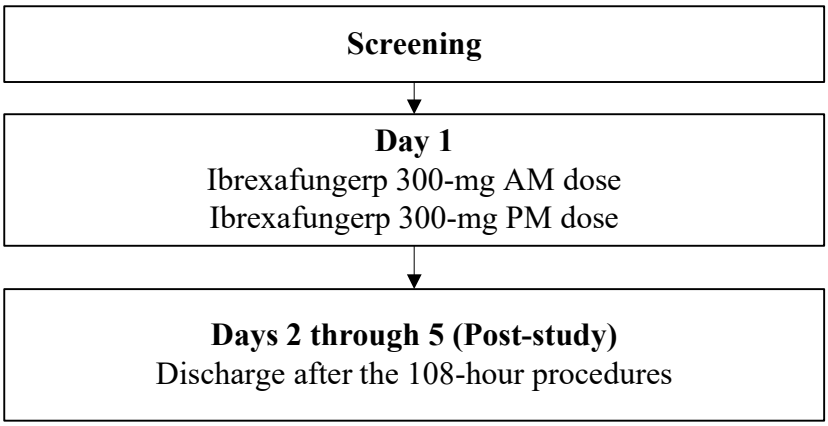
Participants will take ibrexafungerp on Day 1 Q12H with food following the schedule below in Table 2.

Table 2: Ibrexafungerp Dosing Schedule

Product, Dose, and Timing	Study Day
Ibrexafungerp 300-mg BID on Day 1	1

A complete schedule of assessments is provided in Table 5. A schematic of the study design is provided in Figure 1.

Figure 1: Study Design



9.2. Number of Participants

Up to 10 healthy lactating females who are at least 10 days postpartum with a full milk supply established and are between the ages of 18 and 50 years, inclusive, at the time of screening. Enough participants will be enrolled to complete up to 10 evaluable participants.

9.3. Criteria for Study Termination

The principal investigator, the sponsor, the appropriate regulatory authorities, and the ethics committee (EC) each reserve the right to terminate the study in the interest of participants' safety and welfare. The sponsor reserves the right to terminate the study at any time for administrative reasons.

9.4. Potential Risks and Discomforts

9.4.1. Potential Risks

Ibrexafungerp at the one day of 2 X 150-mg dose may cause some side effects. Participants will be notified that they may experience none, some, or all of the side effects listed below because medicine can affect individual people in different ways. In addition, the study medication may involve risks that are currently unknown. Participants will be asked to tell the study staff immediately if they experience any side effects while participating in this study, however minor.

Potentials risks of ibrexafungerp:

- gastrointestinal (diarrhea, abdominal pain, nausea, and vomiting);
- elevation in liver enzymes (AST/ALT);
- hypersensitivity reactions;

The risks of interruption of breastfeeding:

- potential for changes in milk supply
- difficulty re-establishing breastfeeding after the study completion

9.4.2. Potential Discomforts

Participants may feel discomfort during some of these tests or may experience some inconveniences. Some may also have risks, which may include:

- Blood samples: drawing blood from your arm may cause pain, bruising, lightheadedness, and rarely infection
- Electrocardiogram (ECG): ECG patches may cause a skin reaction such as redness or itching
- Breast Pump Usage (Medela, 2022): Pumping breastmilk shouldn't hurt, but participants may feel discomfort while expressing breastmilk, or get blisters or chafing on their nipples or breasts.
  - Note: a lactation specialist will be available to answer any participant questions or concerns.

10. SELECTION AND WITHDRAWAL OF PARTICIPANTS

10.1. Participant Selection Criteria

10.1.1. Inclusion Criteria

A female will be included in the study if she meets the following inclusion criteria if the participant:

1. is a healthy lactating woman aged 18 to 50 years, inclusive, at Screening.
2. is at least 10-days postpartum after uncomplicated delivery with a full milk supply established. (There is no specific length of time postpartum).
3. is actively breastfeeding or expressing breast milk.
4. is willing to temporarily discontinue breast feeding their infant before the Day 1 morning dose through to 108 hours after the first dose (approximately 4.5 days) AND has the ability to pump breast milk and to provide a reserve for infant feeding, with acceptance of bottle feeding, prior to the study.

   OR

   has decided to discontinue breastfeeding permanently but has not yet started weaning their infant with acceptance of bottle feeding for the infant. Participants must have an adequate milk supply (if pumping at least 3 to 4 times a day) as milk composition changes during the weaning process.

   Note: Care should be taken to ensure that participants have not discontinued breastfeeding an infant in order to participate in the study.

   Note: Alternative infant nutrition (previously stored breastmilk or infant formula) should be available for feeding the infant from study Day 1 through 96 hours after the second dose (108 hours after the first dose).

   Note: A lactation specialist will be available for participant support during the study.
5. is willing to fully express breast milk from both breasts during the duration of the milk collection portion of the study. Participants must be able to express milk from each breast at each pumping session using an electric breast pump.
6. has a Body Mass Index (BMI) $\leq$34 kg/m^2 at the screening visit. BMI is calculated by taking the participant's weight in kg and dividing by the participant's height in meters, squared.
7. is judged to be in good health based on medical history, physical examination, vital sign measurements, and laboratory safety tests (all within laboratory normal ranges or changes outside the normal range judged to be clinically non-significant by the investigator) performed at the screening visit and prior to administration of the initial dose of study drug.
8. has no clinically significant abnormality on electrocardiogram (ECG) performed at the screening visit.

9. has been a non-smoker (including vaping) or a light smoker (less than 10 cigarettes per day) for at least 6 months.
10. understands the study procedures and agrees to participate in the study by giving written informed consent.
11. is willing to comply with the study restrictions and participate for the full length of the study for a complete summary of study restrictions see Section 11.3.
12. is not pregnant and highly unlikely to become pregnant.
    a. A female participant who is of reproductive potential agrees to remain abstinent or use (or have their partner use) 2 acceptable methods of contraception starting from the time of consent through the post-study visit. Acceptable methods of birth control for female participants are intrauterine device, diaphragm with spermicide, contraceptive sponge, and condom. For female participants, oral contraceptive pills (OCP) are not to be used as contraception as the effect of ibrexafungerp on the efficacy of OCP has not yet been established.
    b. Women of childbearing potential must have a negative serum pregnancy test (β human chorionic gonadotropin [β-hCG]) prior to enrolment (performed by the site's local laboratory).

10.1.2. Exclusion Criteria

A female will be excluded from participation in the study if they meet any of the following exclusion criteria if the participant:

1. is pregnant or unwilling or unable to comply with the lifestyle guidelines presented in the protocol during the study period and through the Post-Study visit.
2. has evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric (including post-natal depression), neurologic, allergic disease (including drug allergies, but excluding untreated asymptomatic, seasonal allergies at time of dosing), or a history of neoplastic disease or any active cancer.
3. is mentally or legally incapacitated.
4. has a history of any illness or clinical findings that, in the opinion of the study investigator, might confound the results of the study or poses an additional risk to the participant or infant by participation in the study.
5. anticipates the use of prescription or non-prescription drugs that are strong CYP3A4 inducers, including vitamins, herbal and dietary supplements (including St. John's Wort) within 7 days of study drug administration (or 14 days if the drug is a potential enzyme inducer), see the list of excluded concomitant medication examples in Appendix C.
6. is unable to refrain from consumption of grapefruit juice, grapefruits, grapefruit products, star fruit, Seville and blood oranges, apple and mulberry juice as well as vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, and mustard), charbroiled meats, and fenugreek beginning

approximately 7 days prior to administration of the initial dose of study drug and throughout the participant's stay in the clinic.

7. consumes significant amounts of alcohol, defined as greater than 2 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [284 mL/10 ounces], wine [125 mL/4 ounces] or distilled spirits [25 mL/1 ounce]) per day. Participant is unable to refrain from all alcohol consumption within one week prior to study dosing throughout the study until the final study visit.
8. consumes excessive amounts of caffeine for one month prior to study drug administration, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola or other caffeinated beverages per day.
9. has had major surgery, donated or lost 1 unit of blood (approximately 500 mL) or participated in another investigational study within 30 days or 5½ half-lives of the investigational product prior to the screening. The 30-day window will be derived from the date of the last study procedure (ie, poststudy, AE follow-up, etc.) in the previous study to the screening visit of the current study.
10. has a history of significant multiple and/or severe allergies [including latex allergy, but with exception of seasonal rhinitis (hay fever)] or has had an anaphylactic reaction or significant intolerability to prescription or non-prescription drugs or food.
11. has a known hypersensitivity to ibrexafungerp.
12. is currently a user including illicit drugs or has a history of drug (including alcohol) abuse within approximately 1 year.
13. is unable to abstain from strenuous exercise from the screening visit until administration of the initial dose of study drug, throughout the study until the poststudy visit.

10.2. Participant Withdrawal Criteria

A participant may be prematurely withdrawn from the study if they develop a toxicity or concurrent illness that, in the investigator's judgment, precludes further participation in the study for the following reasons:

- Occurrence of an AE that, in the judgment of the investigator, warrants withdrawal of the participant from the study drug;

A participant may also be permanently withdrawn from the study for any of the following reasons:

- Pregnancy
- Non-compliance (not completing all required assessments at required times, or missing scheduled visits) or protocol violation;
- Withdrawal of consent and refusal to participate further in the study;
- Investigator or Sponsor decision that withdrawal is in the participant's best interest;
- Termination of the study by the Sponsor or health authority;

- Lost to follow-up;
- Administrative decision of sponsor.

If a participant is to be labeled as lost to follow-up the site is required to make efforts to contact the participant following a missed visit.

All participants who withdraw from the study will be followed up and data collection will continue for all available information collected per protocol.

Participants who discontinue or are discontinued may be replaced at the discretion of the investigator and Sponsor to ensure that up to 10 evaluable participants complete the study.

11. TREATMENT OF PARTICIPANTS

11.1. Description of Study Drug

The Sponsor will provide the study site with adequate clinical supplies including: 150-mg ibrexafungerp tablets of the citrate salt formulation (Table 3).

Table 3: Investigational Product

	Investigational Product
Product Name:	Ibrexafungerp tablets (as citrate salt)
Dosage Form:	150-mg ibrexafungerp tablets (as citrate salt)
Unit Dose:	2 X 150-mg tablets for the 300-mg dose
Route of Administration:	Oral
Physical Description:	150-mg compressed tablets
Manufacturer:	SCYNEXIS, Inc.

11.2. Prior and Concomitant Medications

All medications (including prescription and over-the-counter (OTC) medications, supplements, and herbal products) taken within 14 days before dosing (Day 1) and through post-study assessments will be recorded on the electronic case report form (eCRF). The identity of the therapy, the dose, route, and regimen, the dates started and stopped (or continuing), and the reason for use must be recorded on an eCRF. If a participant is not able to discontinue all prior medications within 14 days or 5 half-lives prior to administration of the initial dose of study medication, and they have been approved by the SCYNEXIS medical monitor, these medications will be noted on the prior medication forms.

Appendix C is a list of prohibited medications for this study. Sunflower lecithin, malta goya, and other herbal fenugreek-free products may be utilized to increase milk production and may be allowed at the discretion of the Investigator after consultation and approval with the SCYNEXIS, Inc. clinical monitor. These supplements and other medications if used must be recorded on the eCRF. Acetaminophen may be used for minor ailments at the discretion of the investigator without prior consultation with the SCYNEXIS, Inc. clinical monitor. Additionally, medication

(other than those in Appendix C) that a participant cannot stop may be allowed at the discretion of the Investigator after consultation and approval with the SCYNEXIS, Inc. clinical monitor. Best medical judgement by the investigator as to how to treat AEs is primary, however if time permits the investigator should consult with the medical monitor when concomitant medications are being considered. The use of any concomitant medication must relate to an AE or the participant's medical history and must be recorded on eCRF as described above.

11.3. Study Restrictions

11.3.1. Alcohol Restrictions

Participants will refrain from all consumption of alcohol within 1 week prior to dosing, throughout the study, and through the final study visit.

11.3.2. Caffeine Restrictions

Participants will refrain from the consumption of caffeine while in the clinical research unit.

11.3.3. Smoking Restrictions

Only non-smokers or light smokers (participants smoking less than 10 cigarettes/day) are permitted to participate. Participants will not be allowed to smoke during the admission period.

11.3.4. Activity Restrictions

Participants will avoid all unusual or strenuous physical activity (ie, running/bicycling races, weightlifting, etc.) from the prestudy (screening) visit, while in the clinical research unit, until the poststudy visit. Participants will be questioned as to the physical activity at prestudy.

Participants will be resting in an undisturbed environment in the supine or semi-recumbent position for at least 10 minutes prior to vital signs or ECG collection.

11.3.5. Breast Feeding

Participants must refrain from all infant breast feeding from prior to dosing on study Day 1 through Day 5 (96 hours after the second dose). Alternative infant nutrition (previously stored breastmilk or infant formula) will be used for feeding the infant during this time period, with acceptance of bottle feeding prior to study start. If a participant discontinues from the trial early for any reason, she must not breast feed her infant until after Day 5 or 96 hours after the second dose of study drug.

11.3.6. Contraception

Female participants who are of reproductive potential must not be pregnant or planning to become pregnant. If participants are of reproductive potential they must agree to; 1.) remain abstinent (true abstinence is defined as abstaining from heterosexual sex and the preferred and usual lifestyle of the participant or 2.) use (or have their partner use) 2 acceptable methods of contraception starting from the time of consent through 96 hours after the completion of study therapy.

Acceptable methods of birth control are non-hormonal intrauterine device, diaphragm with, contraceptive sponge, condom, and vasectomy. Oral contraceptive pills are not to be relied upon as an acceptable method of contraception since the effect of ibrexafungerp on the efficacy of oral contraceptive pills has not yet been established.

NOTE: Women of childbearing potential must have a negative pregnancy test (β human chorionic gonadotropin [β-hCG]) at Screening visit and at admission to the clinic.

11.4. Treatment Compliance

All doses of study drug will be administered in the clinical unit under direct observation of clinic personnel and recorded in the eCRF. Clinic personnel will confirm that the participant has swallowed the entire dose of study drug by mouth check. If a participant does not swallow the entire dose of study drug, the amount taken and the reason for the incomplete or missed dose will be recorded.

The date and exact time of study drug dosing will be recorded on the appropriate page of the eCRF. If a participant does not receive study drug, the reason for the missed dose will be recorded.

11.5. Standard Meals (in clinic)

11.5.1. Standard Meal

Participants will start to consume a standard meal approximately 30 minutes prior to and finish prior to the administration of the ibrexafungerp dose. The clinical research unit will determine the actual content of the standard meals, the meals should fit into the standard meal definition provided below in Table 4. All participants are expected to consume the same meal with regards to kcal and fat content prior to the AM and PM doses.

Table 4: Standard Meal Definition

Meal Type	Total calories	Fat		
		Kcal	Grams	Percent
Standard	~600 - 800	~132 – 420	~16 - 47	~27 - 42

Other Standardized Meals and Restrictions

While in the research unit, a standardized lunch will be provided at 4 hours and a snack at 8 hours post AM dose, another snack will be offered at 14 hours post AM dose. The caloric content and composition of meals and snacks will be the same for all participants while in the clinical research unit.

11.6. Randomization and Blinding

This is an open-label study. Each participant will be assigned a participant's study number (in numerical order as they are enrolled) prior to dosing. The participant's study number will be used to identify the participant for all procedures and in eCRF. A single participant cannot be assigned more than 1 participant study number.

11.7. Study Procedures

The following sections provide a description of the individual study procedures to be performed during the conduct of the study. A detailed schedule of all study procedures is presented in the Schedule of Assessments Table 5. See Appendix A for time windows for vital signs and PK sampling.

Study procedures should be completed as close to the prescribed/scheduled time as possible. Procedures will be performed in the following priority of proximity (below) with regard to the prescribed time. For this study the blood samples for ibrexafungerp are the critical parameter and needs to be collected as close to the exact time point as possible.

- Breast milk sample collection for ibrexafungerp
- Plasma sample collection for ibrexafungerp
- Laboratory safety tests
- Vital signs
- Physical examinations, (if appropriate)
- Standard Meals

The order of priority can be changed during the study with joint agreement of the investigator and SCYNEXIS, Inc.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

11.7.1. Prestudy Screening (Day -28 to Day -1)

Screening and Day -1 procedures can be completed together the same day depending on when the participant is screened and able to be treated. Prestudy screening will occur within approximately 4 weeks prior to administration of the initial dose of study medication. Potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in the inclusion and exclusion criteria. The investigator will discuss with each participant the nature of the study, its requirements, and its restrictions.

Prestudy screening will include the following procedures:

- Provision of written informed consent
- Adverse event surveillance from the time informed consent is obtained
- Review of inclusion/exclusion criteria
- Demographics information
- Medical history for the prior 1 year (including pregnancy, postpartum, and lactation history)
- Prior Medication review
- Physical examination, including body weight and height

- Vital signs (HR/BP/RR/Temp)
- 12-lead ECG
- Laboratory safety tests
- HIV/Hepatitis Screen
- Pregnancy test (serum)
- COVID, Alcohol and urine drug screen (site standard)

For details on the procedures, please refer to the Schedule of Assessments (Table 5).

11.7.2. Predose (Prior to Day 1 Morning Dosing)

Predose is considered up to 12 hours prior to dosing (Day 1, time 0), therefore exams and tests to be done "predose" can be completed up to 12 hours prior to dosing (time 0). Predose safety labs and serum pregnancy test can be obtained up to 24-48 hours predose.

Prior to treatment, the clinical and laboratory safety parameter values will be reviewed by the Investigator and discussed with the Sponsor if parameters are outside the normal range and considered clinically significant.

Safety laboratory results should be known and reviewed prior to Day 1 dose. Participants shall report to the clinical research unit predose. The following procedures will be performed predose Day 1:

- Admission to Clinic (for participant, and infant if that is the participant's choice). Infant admission is not mandatory, but the site will provide this option.
- Review of inclusion/ exclusion criteria
- Adverse event surveillance
- Concomitant medication review
- Physical examination
- Laboratory safety tests (only hematology, AST, ALT, and bilirubin will be assessed)
- Vital signs (HR/BP/RR/Temp)
- Pregnancy test (serum), if screening was more than 24-48 hours prior to Day 1 dosing
- COVID, Alcohol and urine drug screen (site standard), if screening was more than 12 hours prior to Day 1 dosing
- Standard meals for participants (if appropriate after admission)
- Infant feeding (previously stored breastmilk or infant formula) should be available for feeding the infant while housed with the participant in the clinical research unit.
- Enrollment, participant number assignment (after all predose procedures are completed)

For details on the procedures, please refer to the Schedule of Assessments (Table 5).

11.7.3. Treatment Day 1

Day 1, time 0 is the Day 1 AM dosage administration. The following procedures will be performed as noted in Table 5:

- A standard meal with start to be consumed 30 minutes prior to the administration of study medication (at -30 minutes and 11.5 hours). Standard meals throughout the rest of the day will be provided for the participant.
- Infant feeding (previously stored breastmilk or infant formula) should be available for feeding the infant while housed with the participant in the clinical research unit.
- Ibrexafungerp 300-mg will be administered orally, at zero hour and at 12 hours, while the participant is in a semi-supine position with 240 mL of room temperature water. A mouth check will be performed to ensure dosing compliance.
- Adverse event surveillance
- Concomitant medication surveillance
- Vital signs (HR/BP)
- Breast milk sample collections for ibrexafungerp
- Plasma sample collections for ibrexafungerp

11.7.4. Day 2 (24-hours postdose) through Day 4

- Standard meals will be provided for the participant.
- Infant feeding (previously stored breastmilk or infant formula) should be available for feeding the infant while housed with the participant in the clinical research unit.
- Adverse event surveillance
- Concomitant medication surveillance
- Breast milk sample collections for ibrexafungerp
- Plasma sample collections for ibrexafungerp

11.7.5. Day 5 (Post-Study)

Prior to the Day 5 discharge from the clinic the following post-study procedures will be performed as noted in Table 5:

- Standard meals will be provided for the participant.
- Adverse event surveillance
- Concomitant medication surveillance
- Physical examination, including body weight
- Vital signs (HR/BP/RR/Temperature)
- Laboratory safety tests (Only hematology and clinical chemistry [coagulation not required])
- Pregnancy test (serum)

Table 5: Schedule of Assessments

Study Procedures	Screening[a]	Day 1					Day 2	Day 3	Day 4	Day 5 Post-study
		Predose[b]	0 hr	8 hr	12 hr	24 hr	36 hr	48 hr	72 hr	108 hr
Informed Consent	X									
Inclusion/Exclusion	X	X								
Physical Exam[c]	X	X								X
12-Lead ECG[c]	X									
Enrollment		X								
Demographics and Medical History prior 1 yr (including pregnancy, postpartum, and lactation history)	X									
Height and Weight[d]	X									X
Vital Signs (HR, BP)[c]	X	X		X		X				X
Vital Signs (RR, Temperature)	X	X								X
Safety laboratory testing[e]	X	X								X
HIV/Hepatitis Screen	X									
COVID, Alcohol, and Urine drug screen (standard at site)[f]	X	X								
Pregnancy Tests (serum)	X	X[j]								X
Standard Meals		X----------								----------X
Study Drug Administration[g]			X		X					
Blood Samples for Ibrexafungerp Concentration[h]			X----------							----------X
Breast Milk Samples for Ibrexafungerp Concentration[i]			X----------							----------X

Table 5: Schedule of Assessments (Continued)

Study Procedures	Screening[a]	Day 1					Day 2	Day 3	Day 4	Day 5 Poststudy
		Predose[b]	0 hr	8 hr	12 hr	24 hr	36 hr	48 hr	72 hr	108 hr
Admission to Clinic and Discharge from Clinic[k]		X								X
Adverse Event Monitoring	X----------X									
Prior/Concomitant Medication	X----------X									

Abbreviations: BP = blood pressure; HR = heart rate; RR = respiratory rate, PK = pharmacokinetic, ECG = electrocardiogram, and HIV = human immunodeficiency virus

[a] Pre-study screening to determine eligibility may be performed within 4 weeks prior to dosing with study medication.

[b] The Day 1 predose examinations and assessments may be performed up to 12 hours predose.

[c] During physical examination at screening and predose participants will also be asked about physical activity. Prior to ECG the participants must be in a semi-recumbent position for at least 10 minutes prior to having heart rate, blood pressure, and ECG performed.

[d] Height documented at screening only.

[e] Participants will not be required to fast prior to collecting blood and urine for laboratory safety tests. At screening a full set of laboratory tests (hematology, coagulation, chemistry, and urinalysis) will be assessed; at pre-dose only hematology, AST, ALT, and bilirubin will be assessed; and at poststudy only hematology and clinical chemistry will be assessed (coagulation will not be required).

[f] Urine drug and alcohol screening will be done at screening, within 12 hours before the first dose, and upon admission to the clinic. COVID-19 testing will be done per site requirements.

[g] Ibrexafungerp 300-mg will be administered BID Q12H on Day 1 while the participant is in a semi-supine position with 240 mL of room temperature water.

[h] Plasma samples will be obtained at the following timepoints: 0 hours (prior to first dose), and at 2, 6, 8, 12, 24, 36, 48, 72 and 108 hours post first dose of study drug for determination of ibrexafungerp in plasma concentrations. The 12-hour samples will be taken prior to the second dose of ibrexafungerp.

[i] Breast Milk: **complete expression** of milk from both breasts (using a standard electric breast pump) will be obtained at the following timepoint and intervals: pre-dose, 0-2, 2-4, 4-8, 8-12, 12-18, 18-24, 24-36, 36-48, 48-72, and 72-108 hours post first dose of study drug.

[j] Pregnancy test to be repeated if screening was more than 24 hours prior to Day 1 dosing.

[k] Admission to the clinic will be prior to dosing on Day 1 (for participant, and infant if that is the participant's choice). Infant admission is not mandatory, but the site will provide this option. The stay in the clinic will be through the Day 5, 108-hour, post-study procedures are complete.

12. STUDY DRUG MATERIALS AND MANAGEMENT

12.1. Study Drug

Ibrexafungerp (SCY-078) citrate salt drug product will be supplied as 150-mg compressed tablets containing 150 mg of ibrexafungerp active ingredient on a free base basis. The tablet blend also contains calcium phosphate, silicified microcrystalline cellulose, croscarmellose sodium, magnesium stearate (non-bovine), povidone, Poloxamer 407, butylated hydroxyanisole. mannitol, crospovidone, and colloidal silicon dioxide.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, handling, storage, distribution, and usage of these materials in accordance with the protocol and any applicable laws and regulations.

The Investigational products used in the study will be supplied in sufficient quantities for participants and any replacement participants. The investigational supplies of ibrexafungerp citrate salt tablets will be provided by the Sponsor, the tablets will be provided as 150-mg ibrexafungerp tablets.

The following drug supplies will be provided:

Product	**Potency:**
Ibrexafungerp (SCY-078) Citrate Salt Tablets	Ibrexafungerp 150-mg (citrate salt)

The investigational product will be provided as open-label supplies, which will be dispensed by a pharmacist or designee at the site.

12.2. Study Drug Packaging and Labeling

The Sponsor will provide the study site with adequate clinical supplies including: 150-mg ibrexafungerp tablets of the citrate salt formulation.

12.2.1. Bulk Container

The container labels for the initial drug supply may contain information similar to the following:

- Sponsor Name: SCYNEXIS, Inc.
- Study Protocol Number
- Product name and potency: 150-mg ibrexafungerp tablets (as citrate salt)
- Storage conditions: Room Temperature (15° C to 25°C)
- Dosing instructions: Administer per protocol
- Caution Statement: "Caution: New Drug – Limited by Federal (United States) Law to Investigational Use Only”

12.3. Study Drug Storage

The primary investigator (or designee) at the clinical research site will be responsible for the proper storage of the study drugs.

For long-term storage, at the site pharmacy, ibrexafungerp study drug supplies will be kept in a secure area (eg, locked cabinet) and stored at room temperature (15°C to 25°C) and protected from moisture. The site will be required to keep a temperature log to establish a record of compliance with these storage conditions. For short-term storage once dispensed for the participant, ibrexafungerp tablets may be stored under ambient conditions.

12.4. Study Drug Preparation and Administration

Ibrexafungerp will be supplied as open label 150-mg tablets.

Two 150-mg tablets will be administered for the 300-mg doses on Day 1 BID doses. Doses will be administered Q12H. The date and time of dose administration will be recorded on the eCRFs.

Each participant will take their doses in a sitting posture with 240 mL of room temperature water 30 minutes after starting to eat a standard meal.

12.5. Study Drug Accountability

Receipt and dispensing of study medications must be recorded by an authorized person at the investigator's site.

The investigator agrees neither to dispense the study drug from, nor store it at any site(s) other than those listed on the Form Food and Drug Administration (FDA) 1572 or Investigator's Agreement. The investigator agrees that study drug(s) will be dispensed by the investigator or sub-investigator(s) named on the Form FDA 1572 or Investigator's Agreement, or their qualified designees.

Accurate and current accounting of the dispensing of investigational product will be maintained on an ongoing basis by a member of the trial site staff:

- Investigational medicinal product dispensed to each participant will be recorded in the trial-specific accountability log.
- Accountability for any drug returned by participants will also be accounted for.

12.6. Study Drug Handling and Disposal

The following must be kept by the site until after the study has concluded and the sponsor or designee has completed final drug accountability and signed off on drug supply return. The study site should then have the used and unused supplies properly disposed of and fully document this process.

- Unused 150-mg ibrexafungerp Tablets (Citrate Formulation)

Copies of the destruction or drug return records should be returned to the sponsor.

A final inventory of the total amount of investigational products received at the trial site against the amount used and destroyed must be recorded in the accountability log. Inventory records must be readily available for inspection by the trial monitor and/or auditor, and open to government inspection at any time.

13. PHARMACOKINETIC ASSESSMENTS

13.1. Blood Sample Collection

Blood samples will be collected at timepoints specified in the Schedule of Assessments (Table 5).

13.2. Breast Milk Collection

Electronic breast pumps will be provided to the participants. Breast milk samples will be collected at time intervals specified in the Schedule of Assessments (Table 5). The milk should be pumped/expressed completely from both breasts at the time intervals specified. The date, time, and volume of milk expressed will be collected and recorded on the eCRF.

NOTE: No breast milk, after the pumping prior to the Day 1 AM dose through the poststudy visit, should be provided to an infant.

13.3. Sample Data

Individual participant plasma and breast milk concentrations, actual milk and blood sampling times, actual volume of milk collected per interval, actual dosing information (actual time and date of dosing, and actual dose taken), and PK parameters for individuals and the group will be listed in tabular format.

14. ASSESSMENT OF SAFETY

14.1. Safety Parameters

The safety and tolerability of ibrexafungerp will be monitored by clinical assessment of adverse experiences and by clinical and laboratory measurements, including vital signs (heart rate, blood pressure, and temperature), physical examinations, and laboratory safety tests Table 5.

14.1.1. Demographic/Medical History

During screening, a complete medical history for the prior 1 year will be recorded for each participant. Medical history will include previous and current medical diagnoses, major surgical procedures as well as pregnancy, postpartum, and lactation history Table 5.

14.1.2. Vital Signs

Vital signs, including blood pressure (BP systolic and diastolic), heart rate, respiratory rate, and body temperature will be measured at the time points indicated in the Schedule of Assessments in Table 5.

Participants should be resting in a semi-recumbent position for at least 10 minutes prior to having vital sign measurements obtained. Semi-recumbent vital signs will include HR and BP.

The method for temperature collection will be oral or tympanic.

14.1.3. Weight and Height

Weight and height will be measured at the time points indicated in the Schedule of Assessments in Table 5.

Body weight and height will be obtained with the participant's shoes off and jacket or coat removed.

14.1.4. Physical Examination and Physical Activity Questioning

A standard physical examination will be performed at the time points indicated in the Schedule of Assessments in Table 5.

The examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Interim physical examinations will be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

Participants will also be questioned as to any strenuous physical activity done prior to clinical admission. If strenuous physical activity was performed the investigator must notify the Sponsor prior to dosing the participant.

14.1.5. Electrocardiogram (ECG)

A 12-lead ECG will be obtained and evaluated by a physician for the presence of abnormalities at the time points indicated in the Schedule of Assessments in Table 5.

Special care must be taken for proper lead placement. Participants should be resting in a semi-recumbent position for at least 10 minutes prior to having ECG readings obtained.

14.1.6. Laboratory Assessments

Blood and urine samples for laboratory assessments will be collected at the time points indicated in the Schedule of Assessments in Table 5. Participants will not be required to fast prior to collecting blood and urine for laboratory safety tests. At screening a full set of laboratory tests (hematology, coagulation, chemistry and urinalysis) will be assessed; at pre-dose only hematology, AST, ALT, and bilirubin will be assessed; and at poststudy only hematology and clinical chemistry will be assessed (coagulation will not be required).

All laboratory hematology, coagulation, urinalysis, and chemistry values must be within normal limits or not clinically significant as determined by the investigator for the participant to be included in this study. Throughout the study clinical laboratory values will be reviewed by the investigator for significance and consideration as an AE. "Out of Range" values will be determined and reported by the laboratory performing the test as high or low with respect to the normal range for each laboratory value. Clinically significant laboratory test value abnormalities should be reported on the AE page of the eCRF as adverse events if they are determined to be clinically significant by the investigator.

14.1.6.1. Hematology

Hematology includes the following assessments:

White blood cell (WBC) count	Hemoglobin (HgB)

Red blood cell (RBC) count	Hematocrit (Hct)
Platelet count	

Differential white blood cell count will include percentages for segmented neutrophils, lymphocytes, monocytes, eosinophils, and basophils and absolute counts for neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

14.1.6.2. Coagulation

The coagulation profile includes the following assessments:

Prothrombin time (PT)
Activated partial thromboplastin time (aPTT)
Prothrombin time with international normalized ratio (INR)

14.1.6.3. Blood Chemistry

Biochemistry testing includes the following assessments performed (fasting is not required for this study):

Alanine aminotransferase (ALT)	Magnesium
Albumin	Phosphorus
Alkaline phosphatase	Potassium
Aspartate aminotransferase (AST)	Sodium
Bicarbonate	Total bilirubin[a]
Calcium	Total creatine phosphokinase (CPK)
Chloride	Total Protein
Cholesterol	Triglycerides (TG)
Creatinine	Urea
	Gamma-glutamyl transferase (GGT)

[a] Bilirubin will be fractionated if total bilirubin is elevated. For all total bilirubin results above the upper limit of normal, obtain direct bilirubin value, including at screening and poststudy.

14.1.6.4. Urinalysis

Urinalysis includes the following assessments:

Dipstick:	Microscopic:
Protein	WBC
Glucose	RBC
pH	Epithelial cells
	Casts (specify)

14.1.6.5. Alcohol and Urine Drug Screens

Alcohol, and urine drug screens (site standard urine drug screen) will be collected at the time points indicated in the Schedule of Assessments in Table 5.

14.1.6.6. Virus Serology

HIV/Hepatitis screens will be collected at the time points indicated in the Schedule of Assessments in Table 5.

14.1.6.7. Pregnancy Screen

Pregnancy tests will be collected at the time points indicated in the Schedule of Assessments in Table 5. The serum pregnancy testing will have a sensitivity of at least 25 mIU/L.

14.1.6.8. COVID Screen

COVID testing will be performed per the site's protocol at the time points indicated in the Schedule of Assessments in Table 5.

14.1.6.9. Adverse Event and Concomitant Medication Assessments

Adverse events will be collected from the time of informed consent throughout the study, up through the poststudy visit.

All medications (both prescription and OTC) taken within 14 days before dosing with study medication throughout the study, and through poststudy visit will be recorded on the eCRF.

14.1.7. Blood Volume Requirements

Approximately 116.5 mL of blood will be collected from participants (see Table 6).

Table 6: Blood Volume Table

Laboratory Test	Number of Collections	Amount per Collection	Total Amount per Participant
Laboratory safety tests	3	15.5 mL	46.5 mL
Blood for ibrexafungerp concentration	10	4 mL	40 mL
Serum for β-hCG test	3	10 mL	30 mL
TOTAL			116.5[a]

[a] If additional pharmacokinetic and/or safety analysis is necessary, additional blood (up to 25 mL) may be obtained.

14.2. Adverse and Serious Adverse Events

14.2.1. Definition of Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug/study intervention, whether or not related to the study drug/study intervention.

Any laboratory abnormality that is deemed to be clinically significant in the opinion of the investigator will be considered an adverse event and should be recorded in the eCRF, whether or not it is related to study drug.

Stable chronic conditions that are present prior to clinical trial entry and do not worsen are not considered adverse events and will be accounted for in the participant's medical history.

The following can be considered AEs:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition detected or diagnosed after the initiation of treatment with study medication, even though it may have been present prior to the start of the study
- Continuous persistent disease or symptoms present at baseline that worsen after informed consent or following the initiation of treatment with study medication

The following are **not** considered AEs:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, or transfusion); the condition that leads to the procedure is an AE
- Pre-existing disease or conditions present or detected at the start of the study that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalizations for cosmetic surgery or elective surgery or social/convenience admissions)

14.2.1.1. Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase (ie, baseline, treatment, or follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur after any participant has been enrolled, before treatment, during treatment, through the post-study visit following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by SCYNEXIS, Inc.

14.2.1.2. Other Adverse Event (OAE)

OAEs will be identified by the Drug Safety Physician and if applicable also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the participant from the study, will be classified as OAEs. For each OAE, a narrative may be written and included in the Clinical Study Report.

Events of Clinical Interest

The following are considered events of clinical interest (ECIs), and must be reported within 24 hours of the site becoming aware of the ECI:

- Overdose
- ALT or AST >3 x ULN, confirmed by repeat
- Hypersensitivity Reactions

Overdose

An overdose occurs if a participant has taken, accidentally or intentionally, any drug administered as part of the protocol in a dose exceeding that prescribed by the protocol. An overdose (and any associated AE) is considered an ECI and must be reported within 24 hours of the site becoming aware of the overdose.

14.2.2. Unexpected Adverse Event

An AE is considered "unexpected" if it is not listed in the Brexafemme® Package Label, Investigator's Brochure (IB), or is of greater specificity or severity than has been observed with the particular study drug being tested. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator's brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

14.2.3. AE and SAE Follow-up

All AEs and SAEs will be followed to resolution (the participant's health has returned to his or her baseline status or all variables have returned to normal) or until an outcome is reached, stabilization occurs (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained, regardless of whether the participant is still participating in the study. All appropriate therapeutic measures should be undertaken and recorded. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s).

One of the following terms should be used to report the outcome of an event:

Recovered/Resolved: The event has fully recovered. If the event was a worsening of an underlying medical condition, the event is considered recovered when the condition has returned to the initial level.

Not recovered/Not resolved: The event was ongoing at the time of the report.

14.2.4. Medical Emergencies

All equipment, supplies, and the properly skilled medical personnel must be accessible for an adverse event requiring immediate treatment.

After a medical emergency has been safely managed, it needs to be reported as soon as possible, but within 24-hours to the safety physician, the SCYNEXIS, Inc. medical monitor and any

appropriate reporting done to the ethics committee and the appropriate regulatory agencies in the necessary time frames.

14.2.5. Protocol Deviations for an Adverse Event

In the event of an adverse event or medical emergency, allowing departures from the protocol will be decided on a case-by-case basis. The Investigator or other physician in attendance in such an emergency must contact the SCYNEXIS, Inc. medical monitor, as soon as possible after the medical emergency has been managed, to discuss the circumstances of the emergency. The Investigator, in consultation with the SCYNEXIS, Inc. medical monitor, will decide whether the participant should continue to participate in the study. The Investigator and the SCYNEXIS, Inc. medical monitor will document this decision. The Investigator will inform the ethics committee of all protocol deviations in accordance with the ethics committee established procedure. No deviations from the protocol of any type will be made without complying with all ethics committee -established procedures.

14.2.6. Additional Needed Clinical Laboratory Tests

Clinical laboratory tests other than those specified in the protocol may be performed to ensure the safety of the participants. Those circumstances and data (dates, times, tests and all notes and results) will be documented on an eCRF.

14.2.7. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related”.

If the relationship between the AE/SAE and the investigational product is determined to be “possible” or “probable” the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

14.2.8. Recording Adverse Events

Adverse events spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as AEs. However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs will be collected from the time informed consent is obtained up through the poststudy visit. Serious Adverse Event information will be collected from time informed consent is obtained through the poststudy visit. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the

onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the participant to discontinue the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 14.2.1.1. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on SCYNEXIS, Inc.'s pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the participant was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

14.2.9. Reporting Adverse Events

All SAEs will be reported as per Appendix B. All SAEs (related and unrelated) will be recorded from the time informed consent is obtained through 30-days after the last dose of study medication. following the end of treatment exposure. Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to SCYNEXIS., Inc. within 24-hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and email or send a copy by fax to SCYNEXIS, Inc. as per Appendix B.

Additional follow-up information, if required or available, should all be emailed or faxed to SCYNEXIS, Inc. as per Appendix B within one business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or study file.

The clinical research unit is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

15. STATISTICS

15.1. Analytical Plan

All analyses will be conducted in accordance with this study protocol and a Statistical Analysis Plan (SAP) and Tables, Listings, and Figures (TLF) shells which will be prepared and approved by the sponsor prior to database lock. The study objectives are in found in Section 8.

15.2. Sample Size Determination

There is no formal power calculation. The N is based on practical aspects of recruitment in this this population. A sample size of up to 10 participants to complete the study is selected.

15.3. Safety Analyses

All adverse events and other safety evaluations (vital signs and clinical safety laboratory tests) will be listed by participant and tabulated for the total number of participants:

All Participants:

All adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). The treatment emergent adverse events (TEAE) will be summarized by system order class (SOC) and preferred term.

Summary statistics and plots will be generated for other safety parameters, including the absolute values and change from baseline values. Some parameters may need to use log scale. It is expected that both the log scale and back-transformed are needed for reporting. No statistical testing will be performed for the safety analysis.

15.4. Pharmacokinetic Analysis

Breast milk will be obtained up to 108 hours post dose and blood samples will be obtained starting pre dose the Day 1 morning dose until 108 hours post first dose of study drug for determination of ibrexafungerp concentrations. Sample time points are as follows:

- Breast Milk: complete expression of milk from both breasts (using a standard electric breast pump) will be obtained at the following timepoints and intervals: pre-dose, 0-2, 2-4, 4-8, 8-12, 12-18, 18-24, 24-36, 36-48, 48-72, and 72-108 hours post first dose of study drug.
- Plasma samples will be obtained at the following timepoints: 0 hours (prior to first dose), and at 2, 6, 8, 12 (prior to second dose), 24, 36, 48, 72, and 108 hours post first dose of study drug for determination of ibrexafungerp in plasma concentrations. The 12-hour samples will be taken prior to the second dose of ibrexafungerp.

The following plasma ibrexafungerp pharmacokinetic parameters: area under the curve (AUC), peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), plasma clearance or apparent oral clearance (CL/F), apparent volume of distribution (V_d), and terminal half-life ($t_{1/2}$) for ibrexafungerp following oral administration of the VVC dosage regimen for ibrexafungerp will be determined for both breast milk and plasma concentrations.

The following PK parameters of ibrexafungerp in breastmilk: AUC for the different collection periods, C_{av} based on AUC derived from collections at different time points; total milk concentration data will be used to calculate C_{max}, C_{min} and T_{max}.

The daily infant dosage (total drug present in milk and consumed by the infant per day) will be calculated:

- Daily Infant Dosage (mg/day) = Σ (total drug concentration in each milk collection multiplied by the expressed milk volume in each milk collection)

The M/P will be calculated. M/P = AUC_{0-24} milk/AUC_{0-24} plasma.

The calculation of M/P should be based on AUC and on multiple time points over 24 hours and not just a single point in time.

The relative infant dose (the percent of the weight-adjusted maternal dosage consumed in breast milk over 24 hours) will be calculated:

- Relative Infant Dose = Infant Dosage (mg/kg/day)/Maternal Dosage (mg/kg/day) multiplied by 100.

Individual participant plasma and breast milk concentrations, actual breast milk and blood sampling dates and times, actual volume of breast milk collected at each time interval, actual dosing information (actual time and date of dosing, and actual dose taken), and PK parameters for individuals and the group will be listed in tabular format. Plasma and breast milk concentrations measured over time will be displayed graphically. Plasma and breast milk concentrations and PK parameters will be summarized using descriptive statistics.

The PK of ibrexafungerp plasma and breastmilk will be assayed using validated LC-MSMS methods.

15.5. Interim Analysis

An interim analysis will be conducted after five participants have completed their participation in the study. The analysis will involve the examination of pharmacokinetic and safety data and will comprise a full analysis as described in the SAP. The objective of the interim analysis is to determine whether the data from 5 participants is sufficient to address the objectives of the study and fulfill the post marketing requirement (PMR 4069-2); if not the study shall continue to recruit up to 10 participants.

The reporting analysis will involve descriptive statistical methods, including summaries, tabulations, graphs, or by-subject listings. Before initiating this analysis, the data for the study endpoints will undergo a thorough cleaning process, and the database will be soft-locked. The SAP will be finalized before database lock.

16. STUDY COMPLETION AND TERMINATION

Study completion is defined as the date the last participant completes the final visit in the study.

Given the unpredictable nature of early Phase 1 studies, it may exceptionally be necessary to keep the study open for gathering/reviewing additional supportive data (preclinical and/or clinical) to optimally complete the objective(s) of the study. In this case, the competent authority

and the ethics committee will be appraised of the maximum extension of the duration of the study beyond the last participant out and the justification for keeping the study open. If necessary, appropriate amendments to the protocol will be generated.

Study termination is defined as a permanent discontinuation of the study due to unanticipated concerns of safety to the study participants or availability of other new data (pharmacokinetic, pharmacodynamic, efficacy, biologic, etc.) arising from clinical or preclinical studies with this study drug. A study may be paused during review of newly available preclinical/clinical safety, pharmacokinetic, pharmacodynamic, efficacy, or biologic data, or other issues of interest or potential concern prior to a final decision for continuation or termination of the study.

16.1. Study Termination

The principal investigator, the sponsor, the regulatory authority, and the IRB/EC each reserve the right to terminate the study in the interest of participant's safety and welfare. The sponsor reserves the right to terminate the study at any time for administrative reasons.

17. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

17.1. Study Monitoring

Before an investigational site can enter a participant into the study SCYNEXIS, Inc. or its responsible CRO will follow their standard operating procedures (SOPs) for site qualification and initiation.

Study progress will be monitored by the sponsor or its representative as frequently as necessary to ensure adequate and accurate data collection, protocol compliance, and study conduct in accordance with accepted regulatory requirements. The principal investigator must make all the participant data available to the study monitor for review during the site monitoring visits. Arrangements for monitoring visits will be made in advance, except in emergency cases.

17.2. Investigator Study Files

The principal investigator is responsible for maintaining all study-related documents in study files. The sponsor will notify the principal investigator when retention of study files is no longer necessary. The following documents will be kept in the study files or be readily accessible:

- original protocol and all amendments;
- signed agreement or protocol;
- signed and dated study staff roles and responsibilities log;
- copy of the current *curriculum vitae* of the principal investigator and of all sub-investigators
- IRB/EC description of the number of members in each category, their area of specialty and qualifications;
- All IRB/EC approvals for the protocol and amendments, informed consent documentation and all updates, advertisements, and written information provided to participants; all IRB/EC correspondence; documentation that the IB and subsequent revisions have been submitted to the IRB/EC; documentation that all SAEs and any

periodic safety reports have been submitted to the IRB/EC; and annual IRB/EC renewals (as required);
- up-to-date laboratory certification and the laboratory's normal values (covering the entire time interval of the study for all laboratory tests conducted during the study);
- all confirmations of investigational drug receipt, drug accountability logs, and drug return records;
- a CD containing final participant eCRF data;
- all correspondence to or from the sponsor or its designees;
- blank informed consent form;
- Investigator's Brochure;
- participant screening log;
- participant list (contains participant initials and/or protocol-specific participant number);
- all participants' original signed informed consents; and,
- monitoring visit log.

17.3. Audits and Inspections

Authorized representatives of SCYNEXIS, Inc., a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an SCYNEXIS, Inc. audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact SCYNEXIS, Inc. immediately if contacted by a regulatory agency about an inspection.

17.4. Institutional Review Board (IRB)/ Ethics Committee (EC)

The Principal Investigator must obtain IRB/EC approval for the investigation. Initial IRB approval, and all materials approved by the IRB/EC for this study including the participant's assent, parental consent forms, and recruitment materials must be maintained by the Investigator and made available for inspection.

18. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, SCYNEXIS, Inc. or its representatives may conduct a quality assurance audit. Please see Section 17.3 for more details regarding the audit process.

19. ETHICS

19.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to SCYNEXIS, Inc. before he or she can enroll any participant into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit participants for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. SCYNEXIS, Inc. will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

19.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements.

19.3. Written Informed Consent

The Principal Investigator(s) or representative(s) at each center will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Participants must also be notified that they are free to discontinue from the study at any time. The participant should be given the opportunity to ask questions and allowed time to consider the information provided.

The participant’s signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the participant.

19.4. Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number to maintain participant confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be performed with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the medical monitor, IRB/EC, the FDA, or the sponsor.

19.5. Financial Disclosure

The financial interests of all investigators from all participating clinical centers must be collected prior to study initiation, immediately after the completion of the final follow-up visit for the last participant, and 1 year following the completion of the clinical trial.

20. DATA HANDLING AND RECORDKEEPING

20.1. Inspection of Records

SCYNEXIS, Inc. or regulatory authorities will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the inspection of the drug storage area, study drug stocks, drug accountability records, participant charts, study source documents, investigator study file documents, and other records relative to study conduct.

20.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 15 years after the end of the trial. If it becomes necessary for SCYNEXIS, Inc. or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

21. LIST OF REFERENCES

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6. FDA Guidance for Industry, Clinical Lactation Studies: Considerations for Study Design Guidance for Industry, May 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-lactation-studies-considerations-study-design
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APPENDIX A. TIME WINDOWS FOR SERIAL ASSESSMENTS

Plasma PK Sampling Timepoints

PK Sampling Timepoint (measured from Day 1 zero hour)	Tolerance Window
<0 hour	-120 minutes to 0 hour
≥0 hour - 108 hour	-5 minutes to +5 minutes

Breast Milk PK Sampling Timepoints

PK Sampling Timepoint (measured from Day 1 zero hour)	Tolerance Window
<0 hour	-20 minutes to 0 hour
≥0 hour - 108 hour	-5 minutes to +5 minutes

Vital Signs and Temperature Timepoints

Vital Signs Timepoint	Tolerance Window
<0 hour	-12 hours to 0 hour
≥0 hour - 108 hour	-20 minutes to +20 minutes

APPENDIX B. SERIOUS ADVERSE EVENT REPORTING

SAEs, as defined in Section 14.2 Adverse and Serious Adverse Events will be reported in accordance with ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Site Responsibilities

All SAEs that occur during the course of the study must be reported to SCYNEXIS within 24 hours of the knowledge of the occurrence.

The Investigator will fill out the SAE form and provide as complete information as are available. At a minimum, participant number, the dates and times of the study drug administered, a narrative description of the event must be provided. An assessment by the Investigator as to the severity of the event and relatedness to study drug should also be provided, if possible. Investigator will report all SAEs to:

[redacted]
sae@scynexis.com
[redacted]

The investigator will report SAE and any follow up information to the Clinical Research Regulatory Council (CRRC) as per the CRRC's procedures and requirements.

The investigator will provide SAE follow-up information as soon as information is available to SCYNEXIS.

SCYNEXIS Responsibilities

If the SAE is considered a Suspected, Unexpected Serious Adverse Reaction (SUSAR) SCYNEXIS will create a Council for International Organizations of Medical Sciences (CIOMS) form or a Medwatch 3500A Report for submission to the relevant regulatory authority within 15-days after SCYNEXIS has learned of the SAE. If the SUSAR is a fatal or life-threatening event, the reports will be sent within 7 days after SCYNEXIS has learned of the event.

Follow-up reports will be provided to regulatory agencies as soon as information is available according to the same reporting periods.

Appendix C. PROHIBITED MEDICATIONS

Strong CYP3A4/5 Inhibitors and CYP3A4/5 Inducers

- **CYP3A4/5 Strong/Moderate Inhibitors**
- **CYP3A4/5 Reversible Inhibitors**

Boceprevir, conivaptan, indinavir, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, telaprevir, telithromycin, itraconazole, posaconazole, and voriconazole

- **CYP3A4/5 Time Dependent Inhibitors**

Clarithromycin, ritonavir, and saquinavir

- **CYP3A4/5 Inducers**

Avasimibe, carbamazepine, phenytoin, rifampin, and St. John’s wort