

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214900Orig1s002

Trade Name: BREXAFEMME®

Generic or Proper Name: ibrexafungerp

Sponsor: Scynexis, Inc.

Approval Date: November 30, 2022

Indication: BREXAFEMME is a triterpenoid antifungal indicated in adult and post-menarchal pediatric females for:

- Treatment of vulvovaginal candidiasis (VVC).
- Reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC).

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER



NDA 214900/S-002

SUPPLEMENT APPROVAL

SCYNEXIS, Inc.
Attention: Glen D. Park, PharmD, MSJ
Vice President, Regulatory Affairs and Quality Assurance
1 Evertrust Plaza, 13th Floor
Jersey City, NJ 07302

Dear Dr. Park:

Please refer to your supplemental new drug application (sNDA) dated and received May 31, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Brexafemme (ibrexafungerp tablets).

This Prior Approval supplemental new drug application provides for the addition of a new indication, for reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC) in adult and post-menarchal pediatric females.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and the Medication Guide) with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling. Information on submitting

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 214900S-002.**” Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for all males and for females ages less than 12 years because necessary studies are impossible or highly impractical since RVVC is an uncommon cause of vulvovaginitis in pre-pubertal girls and does not exist in males.

We note that you have fulfilled the pediatric study requirement for females ages 12 to 17 years for this application.

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.³

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety-related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

³ For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/media/128163/download>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

ENHANCED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for exposure to ibrexafungerp during pregnancy. Submit all confirmed or possible cases of exposure to ibrexafungerp during pregnancy as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)) and include a narrative summary and analysis (as described under 21 CFR 314.80(c)(2)) of exposure during pregnancy as part of your required postmarketing safety reports [e.g., periodic safety reports].

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at 301-796-0797.

Sincerely,

{See appended electronic signature page}

Peter Kim, MD, MS
Director
Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - Medication Guide
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PETER W KIM
11/30/2022 02:01:56 PM

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BREXAFEMME® safely and effectively. See full prescribing information for BREXAFEMME®.

BREXAFEMME® (ibrexafungerp tablets), for oral use
Initial U.S. Approval: 2021

WARNING: RISK OF EMBRYO-FETAL TOXICITY

See full prescribing information for the complete boxed warning.

- BREXAFEMME is contraindicated in pregnancy because it may cause fetal harm based on findings from animal reproductive studies. (4, 5.1)
- For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment. Reassessing pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC). (2.3, 5.1)
- Advise females of reproductive potential to use effective contraception during treatment of vulvovaginal candidiasis (VVC) and throughout the 6-month treatment period for reduction in the incidence of RVVC with BREXAFEMME and for 4 days after the last dose. (5.1, 8.3)

RECENT MAJOR CHANGES

Boxed Warning	11/2022
Indications and Usage (1)	11/2022
Dosage and Administration, (2)	11/2022

INDICATIONS AND USAGE

BREXAFEMME is a triterpenoid antifungal indicated in adult and post-menarchal pediatric females for:

- Treatment of vulvovaginal candidiasis (VVC). (1.1)
- Reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC) (1.1)

DOSAGE AND ADMINISTRATION

- Treatment of VVC: The recommended dosage of BREXAFEMME in adult and post-menarchal pediatric females is 300 mg (two tablets of 150 mg) administered approximately 12 hours apart (e.g., in the morning and in the evening) for one day, for a total daily dosage of 600 mg (four 150 mg tablets). (2.1)

- Reduction in the incidence of RVVC: The recommended dosage of BREXAFEMME in adult and post-menarchal females is 300 mg (two tablets of 150 mg) administered approximately 12 hours apart (e.g., in the morning and in the evening) for one day, for a total daily dosage of 600 mg (four 150 mg tablets) monthly for six months. (2.1)
- BREXAFEMME may be taken with or without food. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 150 mg of ibrexafungerp (3)

CONTRAINDICATIONS

- Pregnancy (4)
- Hypersensitivity to ibrexafungerp. (4)

ADVERSE REACTIONS

- Treatment of VVC: The most frequent adverse reactions (incidence $\geq 2\%$) reported were diarrhea, nausea, abdominal pain, dizziness and vomiting. (6.1)
- Reduction in the incidence of RVVC: The most frequent adverse reactions (incidence $\geq 2\%$) reported were headache, abdominal pain, diarrhea, nausea, urinary tract infection and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact SCYNEXIS, Inc. at 1-888-982-7299 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Concomitant use of strong CYP3A inhibitors increases the exposure of ibrexafungerp. Reduce BREXAFEMME dose with concomitant use of a strong CYP3A inhibitor to 150 mg twice daily for one day. (2.2, 7)
- Concomitant use of strong and moderate CYP3A inducers may significantly reduce the exposure of ibrexafungerp. Avoid concomitant administration of BREXAFEMME with strong or moderate CYP3A inducers. (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF EMBRYO-FETAL TOXICITY

- **BREXAFEMME is contraindicated in pregnancy because it may cause fetal harm based on findings from animal reproductive studies [see Contraindications (4) and Warnings and Precautions (5.1)].**
- **For females of reproductive potential, verify that the patient is not pregnant prior to initiating BREXAFEMME treatment. Reassessing pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC) [see Dosage and Administration (2.3), Warnings and Precautions (5.1) and Use in Specific Populations (8.3)].**
- **Advise females of reproductive potential to use effective contraception during treatment of vulvovaginal candidiasis (VVC) and throughout the 6-month treatment period for reduction in the incidence of RVVC with BREXAFEMME and, for 4 days after the last dose [see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)].**

1 INDICATIONS AND USAGE

1.1 Vulvovaginal Candidiasis

BREXAFEMME® is indicated in adult and post-menarchal pediatric females for:

- Treatment of vulvovaginal candidiasis (VVC)
- Reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC).

1.2 Usage

If specimens for fungal culture are obtained prior to therapy, antifungal therapy may be instituted before the results of the cultures are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Treatment of VVC: The recommended dosage of BREXAFEMME in adult and post-menarchal pediatric females is 300 mg (two 150 mg tablets) administered approximately 12 hours apart (e.g., in the morning and in the evening) for one day, for a total daily dosage of 600 mg (four 150 mg tablets).

Reduction in the Incidence of RVVC: The recommended dosage of BREXAFEMME to prevent recurrences is 300 mg (two 150 mg tablets) administered approximately 12 hours apart (e.g., in the morning and in the evening) for one day, for a total daily dosage of 600 mg (four 150 mg tablets) monthly for six months.

BREXAFEMME may be taken with or without food.

2.2 Dosage Modifications in Patients due to Concomitant Use of a Strong Inhibitor of Cytochrome P450 Isoenzymes (CYP) 3A

With concomitant use of a strong CYP3A inhibitor, administer BREXAFEMME 150 mg approximately 12 hours apart (e.g., in the morning and in the evening) for one day. No dosage adjustment is warranted in patients with concomitant use of a weak or moderate CYP3A inhibitor [see [Drug Interactions \(7\)](#) and [Clinical Pharmacology \(12.3\)](#)].

2.3 Pregnancy Evaluation Prior to Initiating Treatment

For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment with BREXAFEMME. Reassessment of pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the incidence of RVVC [see [Contraindications \(4\)](#), [Warning and Precautions \(5.1\)](#) and [Use in Specific Populations \(8.1, 8.3\)](#)].

3 DOSAGE FORMS AND STRENGTHS

BREXAFEMME tablets are purple, oval, biconvex shaped tablets debossed with 150 on one side and SCYX on the other side containing 150 mg of ibrexafungerp.

4 CONTRAINDICATIONS

BREXAFEMME is contraindicated in:

- Pregnancy [see [Warnings and Precautions \(5.1\)](#), and [Use in Specific Populations \(8.1, 8.3\)](#)]
- Patients with hypersensitivity to ibrexafungerp

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Embryo-Fetal Toxicity

Based on findings from animal studies, BREXAFEMME use is contraindicated in pregnancy because it may cause fetal harm. In animal reproduction studies, ibrexafungerp administered orally to pregnant rabbits during organogenesis was associated with fetal malformations including absent forelimb(s), absent hindpaw, absent ear pinna, and thoracogastroschisis at dose exposures greater or equal to approximately 5 times the human exposure at the recommended human dose (RHD).

For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment with BREXAFEMME. Reassessment of pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the incidence of RVVC. Advise females of reproductive potential to use effective contraception during treatment of VVC and throughout the 6-month treatment period for reduction in the incidence of RVVC with BREXAFEMME and, for 4 days after the last dose [see [Use in Specific Populations \(8.1, 8.3\)](#)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Treatment of VVC

A total of 545 patients were exposed to BREXAFEMME in two clinical trials of post-menarchal females with VVC (Trial 1 and Trial 2). The patients were treated with BREXAFEMME 300 mg (two 150 mg tablets) twice a day, 12 hours apart, for one day. The patients were 18 to 76 years of age (mean 34 years); 69% were White and 28% were Black or African American; 18% were of Hispanic or Latina ethnicity.

The most frequently reported adverse reactions are presented in Table 1.

There were no serious adverse reactions and 2 out of 545 (0.4%) patients discontinued treatment with BREXAFEMME due to vomiting (1 patient) and dizziness (1 patient).

Table 1. Adverse Reactions with Rates $\geq 2\%$ in BREXAFEMME-Treated Patients with VVC in Trials 1 and 2

Adverse Reaction	BREXAFEMME N = 545 n (%)	Placebo N = 275 n (%)
Diarrhea	91 (16.7%)	9 (3.3%)
Nausea	65 (11.9%)	11 (4.0%)
Abdominal pain ¹	62 (11.4%)	14 (5.1%)
Dizziness ²	18 (3.3%)	7 (2.5%)
Vomiting	11 (2.0%)	2 (0.7%)

¹ Includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort

² Includes dizziness and postural dizziness

Other Adverse Reactions

The following adverse reactions occurred in < 2% of patients receiving BREXAFEMME in Trial 1 and Trial 2: dysmenorrhea, flatulence, back pain, elevated transaminases, vaginal bleeding, rash/hypersensitivity reaction.

Reduction in the Incidence of RVVC

A total of 130 patients were exposed to BREXAFEMME in a clinical trial of post-menarchal females with RVVC (Trial 3). The patients were treated with BREXAFEMME 300 mg (two 150 mg tablets) twice a day, 12 hours apart, for one day, monthly for six consecutive months. The patients were 18 to 65 years of age (mean 34 years), of which, 59% of patients were between 18 to 35 years, and 41% between 36 to 65 years. Ninety two percent (92%) were White, 7% were Black or African American, and 1% were Asian. Nine percent (9%) of patients were of Hispanic or Latina ethnicity.

The most frequently reported adverse reactions are presented in Table 2.

There were no serious adverse reactions and no patients discontinued treatment with BREXAFEMME due to adverse reaction.

Table 2. Adverse Reactions with Rates $\geq 2\%$ in BREXAFEMME-Treated Patients with RVVC in Trial 3

Adverse Reaction ¹	BREXAFEMME N = 130 n (%)	Placebo N = 130 n (%)
Headache	23 (17.6)	10 (7.6)
Abdominal pain ²	13 (10.0)	9 (6.9)
Diarrhea	10 (7.7)	5 (3.8)
Nausea	7 (5.4)	5 (3.8)
Urinary tract infection	5 (3.8)	1 (0.8)
Fatigue	4 (3.1)	0

¹ A single patient may have had multiple instances of adverse reactions. Only one episode of adverse reaction is counted per patient.

² Includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort

7 DRUG INTERACTIONS

Ibrexafungerp is a substrate of CYP3A4. Drugs that inhibit or induce CYP3A may alter the plasma concentrations of ibrexafungerp and affect the safety and efficacy of BREXAFEMME [see [Clinical Pharmacology \(12.3\)](#)]

Table 3 Effect of Coadministered Drugs on Ibrexafungerp Pharmacokinetics:

Concomitant Drugs	Effect on Ibrexafungerp Concentration	Recommendation
Strong CYP3A inhibitors: (e.g., ketoconazole, itraconazole)	Significantly increased	Reduce the BREXAFEMME dosage [see Dosage and Administration (2.2)]
Strong and Moderate CYP3A inducers: (e.g., rifampin, carbamazepine, phenytoin, St. John's wort, long acting barbiturates, bosentan, efavirenz, or etravirine)	Not studied in vivo or in vitro, but likely to result in significant reduction	Avoid concomitant administration

Ibrexafungerp is an inhibitor of CYP3A4, P-gp and OATP1B3 transporter [see [Clinical Pharmacology \(12.3\)](#)]. However, given the short treatment duration for VVC, the effect of BREXAFEMME on the pharmacokinetics of substrates of CYP3A4, P-gp and OATP1B3 transporters is not considered to be clinically significant.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies, BREXAFEMME use is contraindicated in pregnancy because it may cause fetal harm. In pregnant rabbits, oral ibrexafungerp administered during

organogenesis was associated with fetal malformations including absent forelimb(s), absent hindpaw, absent ear pinna, and thoracogastroschisis at dose exposures greater or equal to approximately 5 times the human exposure at the RHD. Oral ibrexafungerp administered to pregnant rats during organogenesis was not associated with fetal toxicity or increased fetal malformations at a dose exposure approximately 5 times the human exposure at the RHD (*see Data*). Available data on BREXAFEMME use in pregnant women are insufficient to draw conclusions about any drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

There is a pregnancy safety study for BREXAFEMME. If BREXAFEMME is inadvertently administered during pregnancy or if pregnancy is detected within 4 days after a patient receives BREXAFEMME, pregnant women exposed to BREXAFEMME and healthcare providers should report pregnancies to SCYNEXIS, Inc. at 1-888-982-SCYX (7299).

Data

Animal Data

In a rat embryo-fetal study, ibrexafungerp was administered to pregnant rats by oral gavage from gestation days (GDs) 6 through 17 at doses of 10, 20, 35, and 50 mg/kg/day. No fetal malformations or changes in embryo-fetal survival or fetal body weights occurred with any of the doses of ibrexafungerp up to the high-dose of 50 mg/kg/day (approximately 5 times the RHD based on plasma AUC comparison).

In an embryo-fetal study in rabbits, ibrexafungerp was administered by oral gavage at doses of 10, 25, and 50 mg/kg/day from GD 7 through GD 19. In the mid-dose group administered 25 mg/kg/day (approximately 5 times the RHD based on AUC comparison), fetal malformations, including absent ear pinna, craniorachischisis, thoracogastroschisis, trunk kyphosis, absent forelimbs, absent forepaws, and absent hindpaw occurred in a single fetus. Malformations including absent hindpaw and anencephaly occurred with an increased litter incidence in the high-dose group of 50 mg/kg/day (approximately 13 times the RHD based on AUC comparison), and other malformations occurred in single fetuses and litters including absent ear pinna, thoracogastroschisis, absent forelimb, and absent thyroid gland. No changes in embryo-fetal survival or fetal body weights were observed with any of the ibrexafungerp doses, and fetal malformations were not observed with the 10 mg/kg/day dose of ibrexafungerp (approximately 2 times the RHD based on AUC comparison).

In a pre-postnatal study in rats, ibrexafungerp was administered by oral gavage from GD 6 through the lactation period until lactation day 20 in maternal doses of 10, 20, 35, and 50 mg/kg/day. No maternal toxicity or adverse effects on the survival, growth, behavior, or reproduction of first-generation offspring occurred with any of the ibrexafungerp doses up to the high dose of 50 mg/kg/day (approximately 5 times the RHD based on AUC comparison).

8.2 Lactation

Risk Summary

There are no data on the presence of ibrexafungerp in either human or animal milk, the effects on the breast-fed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BREXAFEMME and any potential adverse effects on the breastfed child from BREXAFEMME or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Based on animal data, BREXAFEMME may cause fetal harm when administered to a pregnant female [see *Use in Specific Populations* (8.1)].

Pregnancy Testing

For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment with BREXAFEMME. Reassessment of pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the incidence of RVVC. [see *Dosage and Administration* (2.3), *Contraindications* (4) and *Use in Specific Populations* (8.1)].

Contraception

Females

For treatment of VVC, advise females of reproductive potential to use effective contraception during treatment with BREXAFEMME and for 4 days after the last dose.

For reduction in the incidence of RVVC, advise females of reproductive potential to use effective contraception throughout the 6-month treatment period with BREXAFEMME and, for 4 days after the last dose.

8.4 Pediatric Use

The safety and effectiveness of BREXAFEMME for treatment of VVC have been established in post-menarchal pediatric females. BREXAFEMME is also indicated for the reduction in the incidence of RVVC [see *Indications and Usage* (1.1)]. Use of BREXAFEMME in post-menarchal pediatric patients is supported by evidence from adequate and well-controlled studies of BREXAFEMME in adult non-pregnant women with additional pharmacokinetic and safety data from post-menarchal pediatric females [see *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3), and *Clinical Studies* (14.1)].

The safety and effectiveness of BREXAFEMME have not been established in pre-menarchal pediatric females.

8.5 Geriatric Use

Clinical studies with ibrexafungerp did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. No clinically meaningful differences in the pharmacokinetics of ibrexafungerp were observed in geriatric patients compared to younger adults [see *Clinical Pharmacology* (12.3)].

8.6 Hepatic Impairment

No dosage adjustment of BREXAFEMME is recommended in patients with mild hepatic impairment (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B).

Administration of BREXAFEMME in patients with severe hepatic impairment (Child-Pugh Class C) has not been studied [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

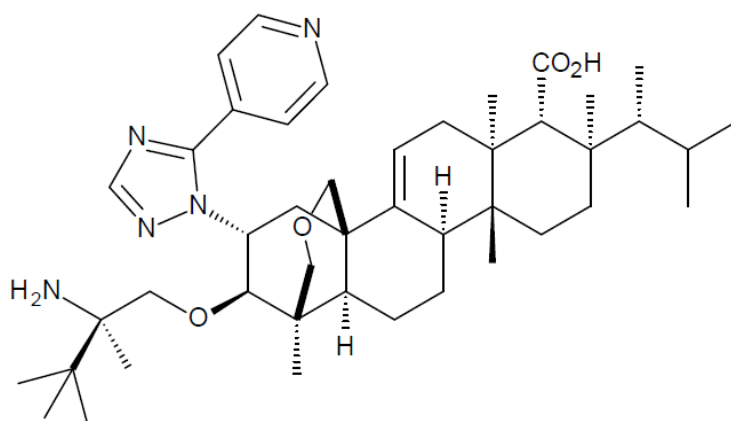
There is no experience with overdosage of BREXAFEMME.

There is no specific antidote for ibrexafungerp. Treatment should be supportive with appropriate monitoring.

11 DESCRIPTION

BREXAFEMME, available as an oral tablet, contains ibrexafungerp citrate, a triterpenoid antifungal agent.

Ibrexafungerp is designated chemically as (1S,4aR,6aS,7R,8R,10aR,10bR,12aR,14R,15R)-15-[(2R)-2-amino-2,3,3-trimethylbutoxy]-1,6a,8,10a-tetramethyl-8-[(2R)-3-methylbutan-2-yl]-14-[5-(pyridine-4-yl)-1H-1,2,4-triazol-1-yl]-1,6,6a,7,8,9,10,10a,10b,11,12,12a-dodecahydro-2H,4H-1,4a-propanophenanthro[1,2-c]pyran-7-carboxylic acid compound with 2-hydroxypropane-1,2,3-tricarboxylic acid (1:1) with an empirical formula of $C_{44}H_{67}N_5O_4 \cdot C_6H_8O_7$ and a molecular weight of 922.18 grams per mole. The chemical structure is:



BREXAFEMME tablet for oral administration is a purple, oval, biconvex shaped, film-coated tablet containing 189.5 mg of ibrexafungerp citrate equivalent to 150 mg of ibrexafungerp. In addition to the active ingredient, the tablet formulation contains butylated hydroxyanisole, colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, and microcrystalline cellulose. The tablet film-coating contains FD&C Blue #2, FD&C Red #40, hydroxypropyl cellulose, hydroxypropylmethyl cellulose 2910, talc and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ibrexafungerp is a triterpenoid antifungal drug [see [Microbiology \(12.4\)](#)].

12.2 Pharmacodynamics

Ibrexafungerp exposure-response relationships and the time course of pharmacodynamic response are unknown.

Cardiac Electrophysiology

At a concentration of 5 times or greater than that achieved after a single day 300 mg twice daily dose, ibrexafungerp does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

In healthy subjects, ibrexafungerp area under the curve (AUC) and maximal concentration ($C_{\max}$) increased approximately dose-proportionally following single dose administration from 10 to 1600 mg (0.02 to 2.67 times the approved recommended daily dose) and multiple-dose administration from 300-800 mg (0.50 to 1.33 times the approved recommended daily dose).

Based on a population pharmacokinetic analysis in patients with VVC, the model predicts that 300 mg twice a day for 2 doses achieves a mean (%CV) AUC_{0-24} exposure of 6832 (15%) ng•hr/mL and $C_{\max}$ of 435 (15%) ng/mL under fasted conditions and a mean AUC_{0-24} exposure of 9867 (15%) ng•h/mL and $C_{\max}$ of 629 (15%) ng/mL under fed conditions.

Absorption

After oral administration of BREXAFEMME in healthy volunteers, ibrexafungerp generally reaches maximum plasma concentrations 4 to 6 hours after single and multiple dosing.

Effect of Food

Following administration of BREXAFEMME to healthy volunteers, the ibrexafungerp $C_{\max}$ increased 32% and the AUC increased 38% with a high fat meal (800-1000 calories; 50% fat), compared to fasted conditions. This exposure change is not considered clinically significant [see [Dosage and Administration \(2.1\)](#)].

Distribution

The mean steady state volume of distribution (V_{ss}) of ibrexafungerp is approximately 600 L. Ibrexafungerp is highly protein bound (greater than 99%), predominantly to albumin. Animal studies demonstrate a 9-fold higher exposure in vaginal tissue than in blood.

Elimination

Ibrexafungerp is eliminated mainly via metabolism and biliary excretion. The elimination half-life is approximately 20 hours.

Metabolism

In vitro studies show that ibrexafungerp undergoes hydroxylation by CYP3A4, followed by glucuronidation and sulfation of a hydroxylated inactive metabolite.

Excretion

Following oral administration of radio-labeled ibrexafungerp to healthy volunteers, a mean of 90% of the radioactive dose (51% as unchanged ibrexafungerp) was recovered in feces and 1% was recovered in urine.

Specific Populations

Post-menarchal Pediatric Females and Geriatric Patients

The pharmacokinetics of ibrexafungerp were not altered in post-menarchal pediatric females (ages 13 to 17 years) or in geriatric patients (ages 65 to 76 years).

Patients with Hepatic Impairment

The pharmacokinetics of ibrexafungerp were not altered in subjects with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment when the total AUC estimates were compared to healthy subjects.

The impact of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of ibrexafungerp is unknown.

Drug Interaction Studies

Ibrexafungerp is a substrate of CYP3A4 and P-gp. In vitro, ibrexafungerp is an inhibitor of CYP2C8, CYP3A4, P-gp transporter, and OATP1B3 transporter. Ibrexafungerp is not an inducer of CYP3A4.

The effect of coadministration of drugs on the pharmacokinetics of ibrexafungerp and the effect of ibrexafungerp on the pharmacokinetics of coadministered drugs were studied in healthy subjects.

Effect of Coadministered Drugs on Ibrexafungerp Pharmacokinetics

Strong CYP3A4 Inhibitor: Ketoconazole (400 mg once daily for 15 days), a strong CYP3A4 and P-gp inhibitor, increased the ibrexafungerp AUC by 5.8-fold and C_{max} by 2.5-fold [see [Drug Interactions \(7\)](#)].

Moderate CYP3A4 Inhibitor: Diltiazem (240 mg once daily for 15 days) increased the ibrexafungerp AUC by 2.5-fold and C_{max} by 2.2-fold. This exposure change is not considered clinically significant at the approved recommended dosage for VVC.

Proton Pump Inhibitor: Pantoprazole (40 mg once daily for 5 days) decreased ibrexafungerp AUC by approximately 25% and C_{max} by 22%. This exposure change is not considered clinically significant at the approved recommended dosage for VVC.

Effect of Ibrexafungerp on the Pharmacokinetics of Coadministered Drugs

The effects of ibrexafungerp on substrates of CYP2C8, CYP3A4, P-gp, and OATP1B3 transporters were evaluated in studies that included loading doses of ibrexafungerp of 1250 to 1500 mg (2.1 to 2.5 times the approved recommended daily dose) for two days followed by 750 mg (1.25 times the approved recommended daily dose) once daily for 3-7 days.

CYP2C8 substrates: Ibrexafungerp did not increase the AUC_{0-inf} or C_{max} of rosiglitazone, a moderate sensitive CYP2C8 substrate.

CYP3A4 substrates: Ibrexafungerp resulted in 1.4-fold increase in the AUC_{0-inf} and no effect on the C_{max} of the sensitive CYP3A4 and P-gp substrate tacrolimus.

P-gp substrates: Ibrexafungerp resulted in a 1.4-fold increase in the AUC_{0-48} and a 1.25-fold increase in the C_{max} of the P-gp substrate dabigatran.

OATP1B3 transporters: Ibrexafungerp resulted in a 2.8-fold increase in the AUC_{0-24} and a 3.5-fold increase in the C_{max} of the OATP1B3 transporter substrate pravastatin.

12.4 Microbiology

Mechanism of Action

Ibrexafungerp, a triterpenoid antifungal agent, inhibits glucan synthase, an enzyme involved in the formation of 1,3- β -D-glucan, an essential component of the fungal cell wall.

Ibrexafungerp has concentration-dependent fungicidal activity against *Candida* species as measured by time kill studies. Ibrexafungerp retains in vitro antifungal activity when tested at pH 4.5 (the normal vaginal pH).

Resistance

The potential for resistance to ibrexafungerp has been evaluated in vitro and is associated with mutations of the *fks-2* gene; the clinical relevance of these findings is unknown. Ibrexafungerp retains activity against most fluconazole resistant *Candida* spp. No resistance development was observed after monthly BREXAFEMME dosing in patients with RVVC.

Interaction with Other Antifungals

In vitro studies have not demonstrated antagonism between ibrexafungerp and azoles or echinocandins.

Antimicrobial Activity

Ibrexafungerp has been shown to be active against most isolates of the following microorganism both in vitro and in clinical infections [see [Indications and Usage \(1\)](#)]:

Candida albicans

The following in vitro data are available, but their clinical significance is unknown. Ibrexafungerp has in vitro activity against most isolates of the following microorganisms:

Candida auris

Candida dubliniensis

Candida glabrata

Candida guilliermondii

Candida kefyr

Candida krusei

Candida lusitanae

Candida parapsilosis

Candida tropicalis

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies of ibrexafungerp have not been performed.

Mutagenesis

No mutagenic or clastogenic effects were detected in an in vitro bacterial reverse mutation assay, an in vitro chromosomal aberration assay, and an in vivo bone marrow micronucleus assay in rats.

Impairment of Fertility

In a male and female fertility study in rats, ibrexafungerp was administered to male rats by oral gavage in doses of 10, 20, 40, and 80 mg/kg/day for 28 days before mating and throughout mating and to female rats for 15 days before mating, during mating, and until gestation day (GD)

6. Ibrexafungerp did not impair fertility in either sex at any dose up to the highest dose of 80 mg/kg/day (approximately 10 times the RHD based on AUC comparison).

13.2 Animal Toxicity and/or Pharmacology

Daily administration of oral ibrexafungerp for 26 weeks in rats, at the highest dose of 80 mg/kg/day (approximately 10 times the RHD based on AUC comparison), was associated with marked, but reversible, phospholipidosis and foamy histiocytes in alveolar tissue in the lung and labored breathing, marked irritation and metaplasia in gastric mucosa, and peripheral nerve degeneration accompanied by hind-limb paralysis.

14 CLINICAL STUDIES

14.1 Treatment of VVC

Two randomized placebo-controlled clinical trials (Trial 1, NCT03734991 and Trial 2, NCT03987620) with a similar design were conducted to evaluate the safety and efficacy of a single day of BREXAFEMME 600 mg (two 150 mg tablets per dose, administered 12 hours apart) for the treatment of VVC. Non-pregnant post-menarchal females with a diagnosis of VVC were eligible. A diagnosis of VVC was defined as (a) minimum composite vulvovaginal signs and symptoms (VSS) score of ≥ 4 with at least two signs or symptoms having a score of 2 (moderate) or greater; (b) positive microscopic examination with 10% KOH in a vaginal sample revealing yeast forms (hyphae/pseudohyphae) or budding yeasts, and (c) normal vaginal pH (≤ 4.5). The total composite VSS score was based on the vulvovaginal signs (erythema, edema, excoriation) and vulvovaginal symptoms (itching, burning, or irritation) where each was scored as 0= absent, 1= mild, 2= moderate, or 3= severe. Study visits included the test of cure (TOC, Day 8 to 14) visit and a follow-up (Day 21 to 29) visit. The modified intent to treat (MITT) population included randomized subjects with a baseline culture positive for *Candida* species who took at least 1 dose of study medication.

Trial 1 was conducted in the United States. The MITT population consisted of 190 patients treated with BREXAFEMME and 100 patients treated with placebo. The average age was 34 years (range 17-67 years), with 91% less than 50 years. Fifty-four percent (54%) were White and 40% were Black or African American, 26% were of Hispanic or Latino ethnicity. The average BMI was 30 and 9% had a history of diabetes. The median VSS score at baseline was 9 (range 4-18). The majority (92%) of the subjects were culture-positive with *C. albicans*.

Trial 2 was conducted in the United States (39%) and Bulgaria (61%). The MITT population consisted of 189 patients treated with BREXAFEMME and 89 patients treated with placebo. The average age was 34 years (range 18-65 years), with 92% less than 50 years. Eighty-one percent (81%) were White and 19% were Black or African American, 10% were of Hispanic or Latino ethnicity. The average BMI was 26 and 5% had a history of diabetes. The median VSS score at baseline was 10 (range 4-18). The majority (89%) of the subjects were culture-positive with *C. albicans*.

Efficacy was assessed by clinical outcome at the TOC visit. A complete clinical response was defined as the complete resolution of signs and symptoms (VSS score of 0). Additional endpoints included a negative culture for *Candida* spp. at the TOC visit, and clinical outcome at the follow-up visit.

Statistically significantly greater percentages of patients experienced a complete clinical response at TOC, negative culture at TOC, and complete clinical response at follow-up with

treatment with BREXAFEMME compared to placebo. The results for the clinical and mycological responses are presented in Table 4.

Table 4. Clinical and Mycological Response in Post-menarchal Females with VVC in Trials 1 and 2, MITT Population

	Trial 1		Trial 2	
	BREXAFEMME N = 190 n (%)	Placebo N = 100 n (%)	BREXAFEMME N = 189 n (%)	Placebo N = 89 n (%)
Complete Clinical Response at TOC¹	95 (50.0)	28 (28.0)	120 (63.5)	40 (44.9)
Difference (95% CI) P-value	22.0 (10.2, 32.8) 0.001		18.6 (6.0, 30.6) 0.009	
Negative Culture at TOC	94 (49.5)	19 (19.0)	111 (58.7)	26 (29.2)
Difference (95% CI) P-value	30.5 (19.4, 40.3) < 0.001		29.5 (17.2, 40.6) < 0.001	
Complete Clinical Response at follow-up²	113 (59.5)	44 (44.0)	137 (72.5)	44 (49.4)
Difference (95% CI) P-value	15.5 (3.4, 27.1) 0.007		23.1 (10.8, 35.0) 0.006	

¹Absence of signs and symptoms (VSS Score of 0) without need for additional antifungal therapy or topical drug therapy for the treatment of vulvovaginal symptoms at test of cure (TOC) visit.

²Absence of signs and symptoms (VSS Score of 0) without need for further antifungal treatment or topical drug therapy for the treatment of vulvovaginal symptoms prior to follow-up visit.

14.2 Reduction in the Incidence of RVVC

A randomized placebo-controlled clinical trial (Trial 3, NCT04029116) was conducted to evaluate the safety and efficacy of BREXAFEMME 300 mg (two 150 mg tablets) administered approximately 12 hours apart (e.g., in the morning and in the evening) for one day, for a total daily dosage of 600 mg (four 150 mg tablets) administered once monthly for six months. Trial 3 was conducted in the United States (33%), Bulgaria (28%), Poland (12%), and Russia (28%). Non-pregnant post-menarchal females presenting with a symptomatic VVC episode and a history of recurrent VVC (at least 3 episodes of VVC in the previous 12 months) were eligible. The symptomatic episode at Screening was treated with 3 doses of fluconazole 150 mg 3 days apart.

To be randomized, patients had to have a culture-confirmed VVC episode at Screening and had to achieve significant resolution of their vulvovaginal signs and symptoms (defined as a total composite score ≤ 2 on the VSS Scale) after fluconazole treatment. Patients were randomized at a 1:1 ratio to receive double-blind BREXAFEMME or placebo administered as a single-day treatment repeated every 4 weeks for a total of 6 single-day treatments. Study visits included the test of cure (TOC) at Week 24 (4 weeks after the last dose) and a follow-up visit at Week 36. The intent to treat (ITT) population was all randomized patients.

The ITT population consisted of 130 patients treated with BREXAFEMME and 130 patients treated with placebo. The average age was 34 years (range 18-65 years) with 95% less than 50 years. Ninety percent (90%) of patients were White, 8% were Black or African American, and 2% were Asian and other race. Eight percent (8%) of patients were of Hispanic or Latino ethnicity. The average BMI of the patient population was 25 and 16.5% were obese (BMI >30).

Efficacy was assessed as the percentage of patients with Clinical Success, defined as subjects with No Culture Proven, Presumed or Suspected Recurrence of VVC requiring antifungal therapy up to TOC at Week 24. Clinical Success was also assessed at the Week 36 Follow-up visit.

Statistically significantly greater percentages of patients experienced Clinical Success at TOC compared to placebo. The clinical success rate at TOC was lower for patients in the United States when compared to patients outside the United States (ex-US) for both BREXAFEMME and placebo groups. In both regions, the BREXAFEMME group had a higher clinical success rate compared to placebo (US: 33% vs 23% and ex-US: 81% vs 68% in BREXAFEMME vs placebo arms, respectively) and the difference between the treatment groups was consistent [US: 10.1% (-9.0, 29.1) and ex-US: 12.9% (0.04, 25.7)]. Clinical Success at Week 36 was also greater for BREXAFEMME compared to placebo. The results for clinical success and reasons for clinical failure are presented in Table 5.

Table 5. Clinical and Mycological Response in Post-menarchal Females with RVVC in Trial 3, ITT Population

	Trial 3		
	BREXAFEMME N = 130 n (%)	Placebo N = 130 n (%)	Difference (95% CI) P-value
Clinical success at TOC (Week 24)	85 (65.4)	69 (53.1)	12.7 (2.2, 23.1) 0.020
Reasons For Clinical Failure at TOC			
Mycologically Proven Recurrence	30 (23.1)	47 (36.2)	
Presumed Recurrence	7 (5.4)	3 (2.3)	
Suspected Recurrence	2 (1.5)	4 (3.1)	
Imputed Recurrence ¹	6 (4.6)	7 (5.4)	
Clinical success at Week 36 Follow Up Visit	75 (57.7)	60 (46.2)	11.9 (1.1, 22.6) 0.034
Reasons For Clinical Failure at Week-36 Follow-up Visit			
Mycologically Proven Recurrence	37 (28.5)	51 (39.2)	
Presumed Recurrence	8 (6.2)	5 (3.8)	
Suspected Recurrence	4 (3.1)	5 (3.8)	
Imputed Recurrence ¹	6 (4.6)	9 (6.9)	

Abbreviations: CI = confidence interval; TOC = test of cure.

¹Imputed recurrences are subjects whose clinical outcome cannot be determined due to early termination or missing critical efficacy assessment at TOC.

16 HOW SUPPLIED / STORAGE AND HANDLING

16.1 How Supplied

BREXAFEMME (ibrexafungerp tablets) are purple, oval, biconvex shaped tablets debossed with 150 on one side and SCYX on the other side. Each tablet contains 150 mg ibrexafungerp (equivalent to 189.5 mg of ibrexafungerp citrate).

Tablets are packaged in polyvinyl/polyvinylidene chloride child-resistant blister packs, four (4) tablets per pack. (NDC 75788-115-04)

16.2 Storage and Handling

Store BREXAFEMME tablets at 20°C to 25°C (68°F to 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA approved patient labeling ([Medication Guide](#))

Risk of Embryo-Fetal Toxicity

- Advise patients that BREXAFEMME is contraindicated in pregnancy since it may cause fetal harm [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1)*].
- Inform females of reproductive potential that their healthcare provider will verify that they are not pregnant prior to initiating BREXAFEMME treatment.
- Advise females of reproductive potential that reassessing pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the incidence of RVVC
- For treatment of VVC, advise females of reproductive potential to use effective contraception while taking BREXAFEMME and for 4 days after the last dose [see *Use in Specific Populations (8.3)*].
- For reduction in the incidence of RVVC, advise females of reproductive potential to use effective contraception throughout the 6-month treatment period with BREXAFEMME and for 4 days after the last dose [see *Use in Specific Populations (8.3)*].
- Advise females to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1)*].
- Advise patients who have inadvertently taken BREXAFEMME during pregnancy that there is a pregnancy safety study that monitors pregnancy outcomes. Encourage these patients to report their pregnancy to SCYNEXIS, Inc. at 1-888-982-7299 [see *Use in Specific Populations (8.1)*].

Important Administration Instructions

For treatment of VVC, inform the patient that each BREXAFEMME dose consists of two tablets. A total treatment course for VVC is two doses taken approximately 12 hours apart and consists of a total of four tablets.

For reduction in the incidence of RVVC, inform the patients that the total treatment course is for six months. Each dose consists of two tablets taken approximately 12 hours apart for a total daily dosage of four tablets, taken monthly for six months.

If the first two tablets are taken in the morning, the second two tablets should be taken that same day in the evening. If the first two tablets are taken in the afternoon or evening, the second two tablets should be taken the following morning.

Inform the patient that BREXAFEMME can be taken with or without food [see *Dosage and Administration (2.1)*].

Concomitant Medications

Advise the patient to inform their health care provider if they are taking any other medications as certain medications can increase or decrease blood concentrations of BREXAFEMME or BREXAFEMME may increase or decrease blood concentrations of certain medications [see *Dosage and Administration (2.2)*].

Manufactured for:
SCYNEXIS, Inc.
Jersey City, NJ

Patent: www.scynexis.com/product/patent

BREXAFEMME® is a registered trademark of SCYNEXIS, Inc.

MEDICATION GUIDE BREXAFEMME® (brex a fem) (ibrexafungerp tablets) for oral use
What is the most important information I should know about BREXAFEMME? BREXAFEMME may cause serious side effects, including: • Harm to your unborn baby. Treatment with BREXAFEMME during pregnancy can cause harm to your unborn baby. Women who can become pregnant may be asked by their healthcare provider to take a pregnancy test before each treatment with BREXAFEMME. Women who can become pregnant should use effective birth control throughout the duration of treatment with BREXAFEMME and for 4 days after the last dose of BREXAFEMME. Talk to your healthcare provider about birth control methods that may be right for you. • See “Do not take BREXAFEMME if you:”
What is BREXAFEMME? • BREXAFEMME is a prescription medicine used to treat vaginal yeast infection and reduce the number of recurrent vaginal yeast infections in adults and adolescent females who have started their menstruation. • It is not known if BREXAFEMME is safe and effective in pre-adolescent females who have not started their menstruation.
Do not take BREXAFEMME if you: • Are pregnant or plan to become pregnant. BREXAFEMME may harm your unborn baby. Tell your healthcare provider if you are pregnant, think you might be pregnant, or plan to become pregnant. • Are allergic to ibrexafungerp.
Before you take BREXAFEMME, tell your healthcare provider about all of your medical conditions, including if you: • Are breastfeeding or plan to breastfeed. It is not known if BREXAFEMME passes into your breast milk. You and your healthcare provider should decide if you will take BREXAFEMME or breast feed. BREXAFEMME may affect the way other medicines work, and other medicines may affect how BREXAFEMME works. Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
How should I take BREXAFEMME? • Take BREXAFEMME exactly as your healthcare provider tells you to take it. • Take BREXAFEMME tablets by mouth with or without food.
What are the possible side effects of BREXAFEMME? • See “What is the most important information I should know about BREXAFEMME?” The most common side effects of BREXAFEMME include headache, loose stools, nausea, stomach pain, dizziness, and vomiting. These are not all the possible side effects of BREXAFEMME. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
How should I store BREXAFEMME? • Store BREXAFEMME at room temperature between 68°F to 77°F (20°C to 25°C). • BREXAFEMME is supplied in child resistant packaging. Keep BREXAFEMME and all medicines out of reach of children.
General information about the safe and effective use of BREXAFEMME. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BREXAFEMME for a condition for which it was not prescribed. Do not give BREXAFEMME to other people even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about BREXAFEMME that is written for health professionals.
What are the ingredients in BREXAFEMME? Active ingredient: ibrexafungerp Inactive ingredients: Tablet core: butylated hydroxyanisole, colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, and microcrystalline cellulose. Tablet film coating: FD&C Blue #2, FD&C Red #40, hydroxypropyl cellulose, hydroxypropylmethyl cellulose 2910, talc and titanium dioxide. BREXAFEMME is a registered trademark of SCYNEXIS, Inc. Manufactured for: SCYNEXIS, Inc., Jersey City, New Jersey, 07302 ©2021 SCYNEXIS, Inc. For more information, call 1-888-982-SCYX (7299) or go to www.brexafemme.com

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214900Orig1s002

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number	NDA 214900 S-002
Priority or Standard	Priority
Submit Date(s)	May 31, 2022
Received Date(s)	May 31, 2022
PDUFA Goal Date	November 30, 2022
Division/Office	Division of Anti-Infectives
Review Completion Date	November 29, 2022
Established/Proper Name	ibrexafungerp
Trade Name	BREXAFEMME
Pharmacologic Class	Triterpenoid antifungal
Code name	SCY-078, MK-3118
Applicant	SCYNEXIS Inc.
Doseage form	Tablets
Applicant proposed Dosing Regimen	300 mg (two tablets of 150 mg) administered by mouth approximately 12 hours apart (e.g., in the morning and in the evening) for one day, for a total daily dosage of 600 mg (four 150 mg tablets) monthly for six months.
Applicant Proposed Indication(s)/Population(s)	'Prevention of recurrent vulvovaginal candidiasis (RVVC) in adult and post-menarchal pediatric females'
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	'Reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC) in adult and post-menarchal pediatric females'
Recommended SNOMED CT Indication Disease Term for each Indication	Recurrent candidiasis of vagina SCTID: 708126004
Recommended Dosing Regimen	300 mg (two tablets of 150 mg) administered approximately 12 hours apart (e.g., in the morning and in the evening) for one day, for a total daily dosage of 600 mg (four 150 mg tablets) monthly for six months

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NDA Multi-disciplinary Review and Evaluation {NDA 214900}
 BREXAFEMME [ibrexafungerp] tablets

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OPQ	Rishi Thakur, PhD, David Lewis, PhD
Microbiology	Simone Shurland, PhD, Avery Goodwin, PhD
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OSI	Cheryl Grandinetti, PharmD, Phillip Kronstein, MD, Jenn Sellers, MD
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DMPP	Mary Carroll, BSN, RN, Marcia Williams, PhD
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OSE/DRM	Laura Zendel, PharmD, Naomi Boston, PharmD
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DCOA	Yasmin Choudhry, MD, Selena Daniels, PharmD, David Reasner, PhD

OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DPMH = Division of Pediatrics and Maternal Health
 DMPP = Division of Medical Policy Programs – Patient Labeling
 DRM = Division of Risk Management
 DCOA = Division of Clinical Outcomes Assessment
 DPV = Division of Pharmacovigilance

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Rama Kapoor, MD	OID/DAI	Sections: 1, 2, 3, 4.1, 6, 7, 8,9 ,10, 11, 12, 13, 14	Select one: ☒ X_ Authored ☐ X_ Approved
	Signature: Rama Kapoor -S Digitally signed by Rama Kapoor -S Date: 2022.11.29 13:09:08 -05'00'			
Statistical Reviewer	Cheryl Dixon, PhD	OB/DBIV	Section: 8.1	Select one: ☒ X_ Authored ☐ X_ Approved
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Statistical Team Leader	Daniel Rubin, PhD	OB/DBIV	Section: 8.1	Select one: ☐ Authored ☒ X_ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Cristina Miglis, PharmD, MS	OTS/OCP/DIDP	Section: 6	Select one: ☒ Authored ☐ Approved
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Clinical Pharmacology Acting Team Leader	Abhay Joshi, PhD	OTS/OCP/DIDP	Section: 6	Select one: ☐ Authored ☒ Approved
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Nonclinical Reviewer	James Wild, PhD	OID/DPTID	Section: 5	Select one: ☒ Authored ☐ Approved
Signature: James Wild -S		Digitally signed by James Wild -S Date: 2022.11.29 14:08:39 -05'00'		
Nonclinical Team Leader	Terry Miller, PhD	OID/DPTID	Section: 5	Select one: ☐ Authored ☒ Approved
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Clinical Microbiology Reviewer	Simone Shurland, PhD	OID/DAI	Section: 4.3	Select one: ☒ Authored ☐ Approved
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Clinical Microbiology Team Leader	Avery Goodwin, PhD	OID/DAI	Section: 4.3	Select one: ☐ Authored ☒ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Deputy Division Director (Clinical)	Dmitri Iarikov, MD, PhD	OID/DAI	Sections: 1-14	Select one: ☐ Authored ☒ Approved
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Division Director (Clinical)	Peter Kim, MD, MS	OID/DAI	Sections: 1-14, 15	Select one: ☒ Authored ☒ Approved
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Associate Director for Labeling	Abimbola Adebawale, PhD	OID/DAI	Section:12	Select one: ☐ Authored ☒ Approved
	Signature: Abimbola O. Adebawale -S Digitally signed by Abimbola O. Adebawale -S Date: 2022.11.29 17:32:06 -05'00'			
Regulatory Project Manager	Alison Rodgers	DRO-ID/DAI	Section: 3	Select one: ☒ Authored ☐ Approved
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Chief, Regulatory Project Management Staff	Gregory DiBernardo	DRO-ID/DAI	Section: 3	Select one: ☐ Authored ☒ Approved
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Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COA	Clinical Outcome Assessment
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FSDS-R	Female Sexual Distress Scale-Revised
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation

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PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
SPA	Special Protocol Assessment
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Ibrexafungerp (BREXAFEMME) oral tablet is a triterpenoid antifungal drug, a semisynthetic derivative of the natural product enfumafungin, which inhibits glucan synthase, an enzyme involved in the formation of the 1,3- β -D-glycan component of the fungal cell wall. Ibrexafungerp was FDA approved on June 1, 2021, for the treatment of adult and postmenarchal pediatric females with vulvovaginal candidiasis (VVC). The approved dosing regimen for treatment of VVC is two 300 mg (two tablets of 150 mg) doses administered orally approximately 12 hours apart for a total daily dosage of 600 mg (four 150 mg tablets).

In this supplemental NDA application, the Applicant, SCYNEXIS, Inc., is seeking approval for the indication of “prevention of recurrent VVC” in postmenarchal females. The proposed dosing regimen for RVVC is 300 mg (two tablets of 150 mg) administered 12 hours apart for one day, every four weeks (once monthly) for a total of up to six months. The dosing regimen for RVVC is similar to VVC except for the duration of treatment, which is one day per month for 6 consecutive months.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Because of the available clinical data on the use of ibrexafungerp in the treatment of VVC, evidence from a single well-designed phase 3 trial (Study SCY-078-304 or Study-304) was deemed adequate to support the efficacy and safety of ibrexafungerp for reduction in the incidence of recurrent VVC. The design of Study 304 followed guidance provided by the Division under a Special Protocol Assessment (SPA) agreement.

The efficacy of ibrexafungerp in the reduction in the incidence of recurrent VVC was evaluated in a multicenter, global, randomized, double-blind, placebo-controlled phase 3 trial. The primary efficacy endpoint was the proportion of patients in the ITT population (patients who received at least one dose of study drug) who had documented clinical success, defined as having a Week 24/Test of Cure (TOC) evaluation and no mycologically proven, presumed or suspected recurrence of VVC up to the TOC visit.

The trial showed statistical superiority of ibrexafungerp over placebo (65.4% versus 53.1%; $P=0.02$) in the proportion of patients with clinical success at TOC. The observed response at TOC was also sustained at the Week 36 or End of Follow Up (EOFU) time point, 4 months after the last dose of study drug. The proportion of patients with no mycologically proven, presumed, or suspected recurrences through Week 36 was nominally significantly higher for the ibrexafungerp arm compared to the placebo arm (57.7% vs 46.2%, $p=0.034$). The reason for

clinical failure in the majority of patients in both treatment arms was a mycologically proven recurrence.

An analysis by geographic region showed that the clinical success rate at TOC was lower for patients in the United States when compared to patients outside the United States (ex-US) for both the ibrexafungerp and placebo treatment arms. However, in both regions, the ibrexafungerp arm had a higher clinical success rate compared to placebo (US: 33% vs 23% and ex-US: 81% vs 68% in ibrexafungerp vs placebo arms, respectively) and the difference between the treatment arms or treatment effect was consistent in both regions [US: 10.1% (-9.0, 29.1) and ex-US: 12.9% (0.04, 25.7)]. These regional differences in efficacy results were not explained by any specific demographic characteristics or disease severity at baseline that may have influenced the response rates between the regions. A similar difference in response rates between US and ex-US sites was observed in the previously conducted phase 3 trials which were the basis for approval of ibrexafungerp for the treatment of VVC.

The safety and effectiveness of oral ibrexafungerp for reduction in the incidence of recurrent VVC in adolescents has been extrapolated from the adult RVVC trial given the similarity in disease pathogenesis and pharmacokinetics (PK) of ibrexafungerp in adolescents and adults.

Notably, there was a previously recognized safety issue related to fetal malformations observed in one species (rabbits) in an animal reproduction study at doses 5 to 13 times higher than the recommended clinical dose. The prescribing information (PI) already includes a warning on the risk of fetal toxicity, and ibrexafungerp is contraindicated in pregnancy. The PI also includes a recommendation to assess pregnancy status prior to administering the dose of ibrexafungerp. Since ibrexafungerp is anticipated to be used by females of reproductive potential and given the intermittent dosing of once a month for six months for the treatment of RVVC, the risk of inadvertent exposure to ibrexafungerp during pregnancy is increased. Therefore, a boxed warning has been added to the labeling to highlight this risk of embryo-fetal toxicity, and a Medication Guide will be provided to patients.

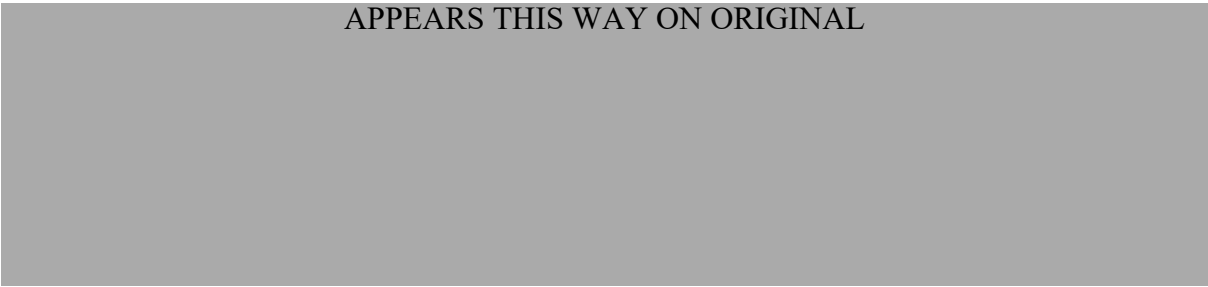
Additional risk mitigation measures included a 'Dear Health Care Provider (DHCP)' letter to inform healthcare providers regarding the need to verify pregnancy status in females of reproductive potential prior to starting ibrexafungerp treatment, advise patients to use effective contraception during treatment of VVC and throughout the 6-month treatment period for reduction in the incidence of RVVC, and the recommendation to reassess pregnancy status prior to each dose when ibrexafungerp is used monthly for 6 months for the reduction in the incidence of RVVC.

Additionally, the Applicant has agreed to perform enhanced pharmacovigilance in the form of postmarketing surveillance for exposure to ibrexafungerp during pregnancy and to submit all confirmed or possible cases of exposure to ibrexafungerp during pregnancy as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)) and include a narrative summary and analysis (as described under 21 CFR 314.80(c)(2)) of exposure during pregnancy as part of required

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postmarketing safety reports [e.g., periodic safety reports].

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit-risk assessment of the information provided in this supplemental NDA supports the approval of ibrexafungerp oral tablets for the reduction in the incidence of RVVC in postmenarchal females at a dose of 300 mg every 12 hours, for 1 day administered monthly, for up to 6 months (a total of 6 single-day treatments, each 4 weeks apart).

Efficacy

The efficacy of ibrexafungerp for the reduction in the incidence of RVVC was evaluated in a global, multicenter, randomized, double-blind, placebo-controlled phase 3 trial (SCY-078-304 or Study-304) enrolling a total of 260 postmenarchal females [ibrexafungerp (n=130); placebo (n=130)] with a history of recurrent VVC, who presented with a culture confirmed symptomatic VVC episode. The symptomatic episode at the Screening visit was first treated with 3 doses of fluconazole 150 mg, with 3 days between each dose. To be randomized in the RVVC trial, patients had to achieve significant resolution of their vulvovaginal signs and symptoms (VSS) (defined as a total composite score ≤ 2 on the VSS Scale). Patients were then randomized at a 1:1 ratio to receive double-blind ibrexafungerp or placebo administered as a single-day treatment repeated every 4 weeks for a total of 6 consecutive single-day treatments.

The primary efficacy endpoint was the proportion of patients in the ITT population (patients who received at least one dose of study drug) who had documented clinical success, defined as having a TOC evaluation and no mycologically proven, presumed or suspected recurrence of VVC up to TOC (Week 24). The trial showed statistical superiority of ibrexafungerp over placebo in the proportion of patients with clinical success at TOC (65.4% versus 53.1%; $P=0.02$). The observed response at TOC was sustained at the End of Follow-Up (EOFU) time point, 4 months after the last dose of study treatment (57.7% vs 46.2%, $p=0.034$). The reason for clinical failure in the majority of patients in both treatment arms was a mycologically proven recurrence.

An analysis by a geographic region showed that the clinical success rate at TOC was lower for patients in the US when compared to patients outside the US (ex-US) for both ibrexafungerp and placebo treatment arms. However, in both regions, the ibrexafungerp arm had a higher clinical success rate compared to placebo (US: 33% vs 23% and ex-US: 81% vs 68% in ibrexafungerp vs. placebo arms, respectively) and the difference between the treatment arms was consistent in both regions [US: 10.1% (-9.0, 29.1) and ex-US: 12.9% (0.04, 25.7)]. This regional difference in efficacy results was not explained by any specific demographic parameters or disease severity at baseline. A similar difference in response rates across regions (US vs. ex-US sites) was observed in previously conducted phase 3 trials that were the basis for approval of ibrexafungerp for the treatment of VVC.

Although the eligibility criteria for the RVVC trial included postmenarchal females 12 years of age and above, the Applicant was unable to enroll postmenarchal females younger than 18 years in this trial. However, given the similarities in PK and disease characteristics in adolescents and

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adults, the efficacy of oral ibrexafungerp in adolescents is extrapolated from adults. Additionally, the safety of oral ibrexafungerp for RVVC treatment is not expected to differ between postmenarchal adolescents and adults.

Safety

A total of 130 patients were exposed to ibrexafungerp in a clinical trial of postmenarchal females with RVVC. The mean age of patients was 34 years (18 to 65 years). Ninety two percent (92%) of patients were White, 7% were Black or African American, and 1% was Asian. Nine percent (9%) of patients were of Hispanic or Latina ethnicity.

There were no deaths in either treatment arm. Two patients (1.5%) in the ibrexafungerp arm experienced SAEs (one patient had 'Covid-19 pneumonia' and 'influenza'; and one patient experienced an SAE of 'adnexa uteri cyst'). Both SAEs were considered not related to study treatment and resolved without sequelae. Treatment emergent adverse events (TEAE) were reported by 63.1% (n=82) of patients in the ibrexafungerp arm and 52.3% (n=68) of patients in the placebo arm. The majority of TEAEs were mild to moderate in severity and were reported at a higher frequency in the ibrexafungerp arm compared to the placebo arm.

The most common adverse drug reactions (incidence $\geq 2\%$) observed with ibrexafungerp were headache (17.6%), abdominal pain (10%), diarrhea (10%), nausea (5.4%), urinary tract infections (3.8%), and fatigue (3.1%). The safety data from the phase 3 trial in RVVC are in line with previously observed adverse events reported in the phase 3 VVC trials, except for the TEAE of headache. Headache (HA) occurred in 8% of patients in the phase 3 VVC trials, and the incidence was similar between the treatment arms. In the RVVC trial, HA was reported with a higher frequency in the ibrexafungerp arm. However, none of the events were serious, and all events resolved between 1-3 days without any sequelae. The reason for this discrepancy is unclear, and it is possible that a longer duration of treatment resulted in higher incidence of HA. Of note, ibrexafungerp does not cross the blood-brain barrier and direct CNS toxicity is not expected. Additionally, the proposed dose regimen for RVVC is 6 instances of one day dosing separated by a month each, and the estimated exposure duration for each dosing period is ~ 4 days (i.e., 5 times the half-life of ibrexafungerp of approximately 20 hours). This regimen would result in an intermittent once-a-month exposure of short duration, and it is expected to be cleared entirely from the plasma and tissue compartments before the next monthly dose is administered. Nevertheless, these AEs will be monitored via routine periodic adverse event reporting.

Oral ibrexafungerp was associated with serious dose-related fetal malformations in a previously conducted rabbit embryo-fetal study at exposures 5 to 13 times the expected clinical exposure. The drug is contraindicated for use in pregnancy. The ibrexafungerp prescribing information already includes a warning on the risk of fetal toxicity and the recommendation to assess pregnancy status prior to administering ibrexafungerp. Additionally, a post marketing pregnancy safety study to collect data in women exposed to ibrexafungerp during pregnancy is currently ongoing (PMR-4069-1).

However, for reduction of RVVC, ibrexafungerp will be used by females of reproductive potential over six months, albeit as a single day treatment each month. Therefore, the risk of inadvertent exposure to ibrexafungerp during pregnancy is increased. To mitigate this risk, a boxed

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warning to highlight the risk of embryo-fetal toxicity has been added, and a Medication Guide will be provided to patients. Additional risk mitigation measures included a “Dear Health Care Provider (DHCP)” letter to inform healthcare providers regarding the need to verify pregnancy status in females of reproductive potential prior to starting ibrexafungerp treatment, advise patients to use effective contraception during treatment of VVC and throughout the 6-month treatment period for reduction in the incidence of RVVC, and the recommendation to reassess pregnancy status prior to each dose when ibrexafungerp is used monthly for 6 months for the reduction in the incidence of RVVC.

Additionally, the Applicant has agreed to perform enhanced pharmacovigilance in the form of postmarketing surveillance for exposure to ibrexafungerp during pregnancy and to submit all confirmed or possible cases of exposure to ibrexafungerp during pregnancy as 15-day “Alert reports” (described under 21 CFR 314.80(c)(1)) and include a narrative summary and analysis (as described under 21 CFR 314.80(c)(2)) of exposure during pregnancy as part of required postmarketing safety reports [e.g., periodic safety reports].

In conclusion, approval of ibrexafungerp for the reduction in the incidence of recurrent VVC in postmenarchal females is supported by the clinical evidence from the phase 3 trial as well as by the data on the efficacy of ibrexafungerp in the treatment of VVC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	- Recurrent vulvovaginal candidiasis is defined as having three or more episodes of VVC within a 12-month period. Approximately 70 to 75% of all females will experience an infection with VVC at least once in their lifetime and up to 9% of these females experience more than three episodes per year. Recurrent VVC affects ~138 million women worldwide, with a global annual prevalence of 3871 per 100,000 women. - The pathogenesis of RVVC is poorly understood and is likely a multifactorial interplay between a genetic predisposition to enhanced vaginal colonization leading to fungal dysbiosis. <i>C. albicans</i> accounts for 85 to 95% of all <i>Candida</i> spp. isolated from the vagina as a cause of VVC and RVVC. - RVVC symptoms range from moderate to severe, but can influence quality of life, increasing stress and decreasing the self-esteem of affected patients.	Recurrent vulvovaginal candidiasis is defined as having three or more episodes of VVC within a 12-month period. Approximately 70 to 75% of all females experiences an infection with VVC at least once in their lifetime and up to 9% of these females experience recurrent VVC. RVVC affects females from all strata of society, with multiple consequences.
<u>Current Treatment Options</u>	- Treatment of RVVC infections is challenging because there are few therapeutic options available. - Oteseconazole (VIVJOA) was approved by the FDA in April 2022 and was the first drug approved for the indication of reduction in incidence of RVVC. Importantly, oteseconazole is contraindicated in females of reproductive potential due to: (1) the findings of severe ocular abnormalities in the offspring of pregnant rats administered oteseconazole, and	There is significant clinical need for a treatment that can reduce the incidence of recurrence of VVC and be used long term with few adverse effects.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(2) its long half-life resulting in a prolonged exposure window of 690 days. - Based on CDC treatment guidelines, oral fluconazole (a 100-mg, 150-mg, or 200-mg dose) weekly for 6 months is recommended as an off-label treatment to reduce the incidence of recurrence of VVC. - In the 10–20% of women with RVVC caused by <i>C. glabrata</i> or other non-albicans <i>Candida</i> species, suppressive therapy with azoles is not as effective.	Oteseconazole is the only drug approved by the FDA for reducing the incidence of RVVC, but its use is restricted to females who are not of reproductive potential.
<u>Benefit</u>	- The efficacy of ibrexafungerp for reduction in the incidence of RVVC was evaluated in a multicenter, global, randomized, double-blind, placebo-controlled phase 3 trial in 260 postmenarchal females with RVVC [ibrexafungerp (n=130); placebo (n=130)]. The primary efficacy endpoint was the proportion of patients in the ITT population who had a documented clinical success defined as having a Week 24 (TOC) evaluation and no mycologically proven, presumed or suspected recurrence of VVC up to TOC. - The mean age of patients was 34 years (18 to 65 years). - The trial showed statistical superiority of ibrexafungerp over placebo in the proportion of patients with clinical success at TOC (65.4% versus 53.1%; P=0.02). The observed response at TOC, was sustained at the Week 36 (EOFU) time point, 4 months after the last dose. The proportion of patients with no mycologically proven, presumed, or suspected recurrences through Week 36 was nominally significantly higher for the ibrexafungerp arm compared to the placebo arm (57.7% vs 46.2%, p=0.034). The majority of clinical failures were due to a mycologically proven recurrence. - An analysis by a geographic region showed a lower clinical success rate at TOC for patients in the US when compared to patients outside the US (ex-US) for both treatment arms. However, in both regions, the ibrexafungerp arm had a higher clinical success rate compared to placebo and the treatment effect was consistent in both regions [US: 33% vs. 23% and ex-US: 81% vs. 68% in ibrexafungerp and placebo arms, respectively. The difference between treatment arms in the US: 10.1% (-9.0, 29.1) and ex-US: 12.9% (0.04, 25.7)]. The reason for a lower clinical success in the US sites was unexplainable by baseline demographics or disease severity. - Efficacy in postmenarchal adolescents is extrapolated from adults.	Ibrexafungerp is effective in reducing the incidence of recurrent VVC in postmenarchal patients with a history of RVVC. *

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk and Risk Management</u>	• There were no deaths in either treatment arm. Two patients (1.5%) in the ibrexafungerp arm experienced SAEs of Covid-19 pneumonia, and uterine adnexal cyst, which were unrelated to treatment and resolved eventually without any sequelae. • Treatment emergent adverse events (TEAE) were reported by 63.1% (n=82) of patients in the ibrexafungerp arm and 52.3% (n=68) of patients in the placebo arm. Overall, the majority of TEAEs were mild to moderate in severity and were reported at a higher frequency in the ibrexafungerp arm compared to the placebo arm. • The most common adverse drug reactions (incidence $\geq 2\%$) observed with ibrexafungerp were headache (17.6%), abdominal pain (10%), diarrhea (10%), nausea (5.4%), urinary tract infections (3.8%), and fatigue (3.1%). • The safety profile of ibrexafungerp in adolescents is not expected to differ from that in adults based on a similar course of disease and similar PK demonstrated in an adolescent PK study. • Ibrexafungerp is a substrate of CYP3A4. Its prescribing information already includes instructions for ibrexafungerp dosage reduction to 150 mg every 12 hours for one day when used with concomitant strong CYP3A inhibitors. The use of ibrexafungerp with moderate and strong CYP3A inducers should be avoided. • Safety in Pregnancy/Risk Mitigation: Addition of Boxed Warning Oral ibrexafungerp was associated with dose-related fetal malformations in one animal species (rabbits) in an embryo-fetal toxicity study at exposures 5- to 13-times the expected clinical exposure. Prescribing information already includes a contraindication for use in pregnancy, a warning on the risk of fetal toxicity, and advises to assess pregnancy status prior to administering ibrexafungerp. Additionally, a post marketing pregnancy safety study in women exposed to ibrexafungerp is currently ongoing (PMR-4069-1). However, the risk of inadvertent exposure during pregnancy is increased with the longer duration of treatment for the indication of RVVC. The proposed dosing regimen for RVVC is 6 single-day monthly treatments, and the estimated exposure for each dosing period is ~ 4 days (i.e., 5 times the half-life of ibrexafungerp of approximately 20 hours). Thus, a boxed warning has been added to highlight the risk of fetal harm, and a Medication Guide will be provided to patients. Additional risk mitigation measures included a "Dear Health Care Provider (DHCP)" letter to inform healthcare providers regarding the need to verify pregnancy status in females of reproductive potential prior to starting ibrexafungerp treatment, advise patients to use effective contraception during treatment of VVC	The most common adverse drug reactions observed with ibrexafungerp were headache, abdominal pain, diarrhea, and nausea. The safety profile in adolescents is expected to be similar to that in adults. Addition of a Boxed Warning: In RVVC, ibrexafungerp will be used as a single-day-a-month dosing for six months, which increases the risk of inadvertent exposure during pregnancy. Thus, a boxed warning has been to highlight the risk of fetal harm. Additional risk mitigation measures included a Medication Guide for patients, communication to healthcare providers (via DHCP letter), and a request for enhanced pharmacovigilance in the form of postmarketing surveillance for exposure to ibrexafungerp during pregnancy as part of required postmarketing safety reports [e.g., periodic safety reports].

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and throughout the 6-month treatment period for reduction in the incidence of RVVC, and the recommendation to reassess pregnancy status prior to each dose when ibrexafungerp is used monthly for 6 months for the reduction in the incidence of RVVC. Additionally, the Applicant has agreed to perform enhanced pharmacovigilance in the form of postmarketing surveillance for exposure to ibrexafungerp during pregnancy and to submit all confirmed or possible cases of exposure to ibrexafungerp during pregnancy as 15-day “Alert reports” (described under 21 CFR 314.80(c)(1)) and include a narrative summary and analysis (as described under 21 CFR 314.80(c)(2)) of exposure during pregnancy as part of required postmarketing safety reports [e.g., periodic safety reports].	

*The Applicant initially proposed an indication for prevention of RVVC. According to the FDA’s draft guidance for industry titled, “Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, (July 2018),” phrases such as “reduce the risk of” or “reduce the incidence of” rather than “prevent” should be considered in the indication.¹ The use of the term “prevent” may imply a guarantee of success.

¹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/indications-and-usage-section-labeling-human-prescription-drug-and-biological-products-content-and>

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	Section 8. Assessment of Effectiveness
☒	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☒	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify):	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☐	Patient experience data was not submitted as part of this application.	

2 Therapeutic Context

2.1. Analysis of Condition

Approximately 75% of women develop VVC at least once in their lifetime, most commonly during the reproductive years. About 9% of these women develop recurrent VVC (RVVC). Recurrent VVC is defined as three or more recurrences of symptomatic VVC within a 12-month period, with completely asymptomatic periods between acute VVC episodes.² A systematic review of literature from 1985 to 2016 estimated that RVVC affects ~138 million women worldwide, with a global annual prevalence of 3871 per 100,000 women.³

Predisposing host factors associated with recurrent VVC are HIV positivity, pregnancy, diabetes mellitus, use of antibacterial drugs, hormone replacement therapy, wearing tight-fitting synthetic clothing, as well as sexual activity.⁴

Pathogenesis of RVVC is poorly understood. Susceptibility to RVVC may include a genetic and immunological predisposition, although in many patients no apparent underlying conditions or predisposing factors are apparent.^{5,6,2} RVVC symptoms range from moderate to severe, but can influence quality of life, increasing the stress and decreasing self-esteem of affected patients.³ *C. albicans* accounts for 85 to 95% of all *Candida spp.* causing VVC and RVVC.^{7,8,9,10} Non-*albicans Candida* species include *Candida glabrata*, *Candida parapsilosis* and *Candida tropicalis*, among other species.¹¹

Diagnosis of an episode of VVC is made by the presence of clinical signs and symptoms of vaginitis and the identification of vaginal yeast by microscopy [wet preparation with saline or

² Sexually transmitted infections treatment guideline, 2021 (2021). www.cdc.gov/std/treatment-guidelines/candidiasis.htm

³ Denning DW, Kneale M, Sobel JD, Rautemaa-Richardson R. Global burden of recurrent vulvovaginal candidiasis: a systematic review. *Lancet Infect. Dis.* 18(11), e339–e347 (2018).

⁴ Blostein F, Levin-Sparenberg E, Wagner J, Foxman B. Recurrent vulvovaginal candidiasis. *Ann. Epidemiol.* 27(9), 575–582.e3 (2017).

⁵ Sobel JD. Recurrent vulvovaginal candidiasis. *Am. J. Obstet. Gynecol.* 214(1), 15–21 (2016).

⁶ Crouss T, Sobel JD, Smith K, Nyirjesy P. Long-term outcomes of women with recurrent vulvovaginal candidiasis after a course of maintenance antifungal therapy. *J. Low. Genit. Tract Dis.* 22(4), 382–386 (2018).

⁷ *National Guideline on the Management of Vulvovaginal Candidiasis*. Clinical Effectiveness Group (British Association for Sexual Health and HIV). <http://www.bashh.org/guidelines/2002/candida%2006%2001.pdf>

⁸ Sobel JD. Vulvovaginal candidosis pathogenesis and treatment. *Lancet* 2007;369:1961–71.

⁹ Foxman B, Muraglia R, Dietz JP, Sobel JD, Wagner J. Prevalence of recurrent vulvovaginal candidiasis in 5 European countries and the United States: Results from an internet panel survey. *J Low Genit Tract Dis* 2013;17:340.

¹⁰ Netea, M.G.; Marodi, L. Innate immune mechanisms for recognition and uptake of *Candida* species. *Trends Immunol.* 2010, 31, 346–353.

¹¹ Sobel JD, Sobel R. Current treatment options for vulvovaginal candidiasis caused by azole-resistant *Candida* species. *Expert Opin. Pharmacother.* 19(9), 971–977 (2018).

potassium hydroxide (KOH)] and culture. VVC is associated with a normal vaginal pH (<4.5).

2.2. Analysis of Current Treatment Options

There has been no FDA approved treatment for reduction in the incidence of recurrent VVC until recently. Oteseconazole (VIVJOA) was the first drug approved by the FDA in April 2022 to reduce the incidence of RVVC in females with a history of RVVC who are not of reproductive potential.¹² Importantly, oteseconazole is contraindicated in females of reproductive potential and in pregnant and lactating women due to: (1) the findings of severe ocular abnormalities in the offspring of pregnant rats administered oteseconazole, and (2) its long half-life resulting in a prolonged exposure window of 690 days.

Treatment of RVVC infections is challenging because there are few therapeutic options¹³. The CDC guidelines² recommend treatment with oral fluconazole (100-, 150-, or 200-mg dose) weekly for 6 months as the first-line maintenance treatment regimen in RVVC in non-pregnant women. Suppressive maintenance therapies are effective at controlling RVVC but are rarely curative long-term.¹⁴ The duration of suppressive therapy is generally recommended for 6 months. However, 30%–50% of women usually recur after maintenance therapy is discontinued.¹⁵ Other off-label therapies for RVVC include vaginal clotrimazole, miconazole, terconazole, and boric acid.^{2, 16, 17, 18}

Notably, long-term use of fluconazole increases the potential for emergence of azole-resistant strains of *C. albicans* and other *Candida* species. Furthermore, in 10–20% of women, RVVC is caused by *C. glabrata* or other non-*albicans Candida* species, where suppressive therapy with azoles is not as effective.¹⁹

¹² VIVJOA (oteseconazole) prescribing information; 4/26/2022.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215888s000lbl.pdf

¹³ Collins LM, Moore R, Sobel JD. Prognosis and long-term outcome of women with idiopathic recurrent vulvovaginal candidiasis caused by *Candida albicans*. J. Low. Genit. Tract Dis. 24(1), 48–52 (2020).

¹⁴ Crouss T, Sobel JD, Smith K, Nyirjesy P. Long-term outcomes of women with recurrent vulvovaginal candidiasis after a course of maintenance antifungal therapy. J Low Genit Tract Dis 2018;22:382–6

¹⁵ Sobel JD, Wiesenfeld HC, Martens M et al. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. N. Engl. J. Med. 351(9), 876–883 (2004).

¹⁶ Fong IW. The value of prophylactic (monthly) clotrimazole versus empiric self-treatment in recurrent vaginal candidiasis. Genitourin Med 1994; 70:124–126.

¹⁷ Stein GE, Mumma NL, Schooley SL. Prevention of recurrent vaginal candidiasis with weekly terconazole cream. Ann Pharmacother 1996;30:1080–1083.

¹⁸ Ringdahl EN. Treatment of recurrent vulvovaginal candidiasis. Am Fam Physician 2000; 61:3306–3312.

¹⁹ Marchaim D, Lemanek L, Bheemreddy S, Kaye KS, Sobel JD. Fluconazole-resistant *Candida albicans* vulvovaginitis. Obstet. Gynecol.120(6), 1407–1414 (2012).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The original NDA 214900 for BREXAFEMME [ibrexafungerp] was approved on June 01, 2021, for the treatment of adult and postmenarchal pediatric females with vulvovaginal candidiasis (VVC).

3.2. Summary of Presubmission/Submission Regulatory Activity

Investigational new drug application (IND) 107521 for MK-3118 (later called SCY-078 and ibrexafungerp) oral formulation was filed on January 12, 2010, by Merck & Co., Inc. On May 24, 2013, Merck transferred ownership of the IND and the rights to all data to SCYNEXIS, Inc.

The application was granted Fast Track designation for the treatment of vulvovaginal candidiasis and recurrent vulvovaginal candidiasis on April 18, 2018.

On April 19, 2018, SCY-078 tablets for oral use were granted Qualified Infectious Disease Product designation for the treatment of vulvovaginal candidiasis and the prevention of recurrent vulvovaginal candidiasis.

Study SCY-078-304, titled, “A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Ibrexafungerp (SCY-078) Compared to Placebo in Subjects with Recurrent Vulvovaginal Candidiasis,” was submitted on February 8, 2019, for a special protocol assessment (SPA). The Division responded with a ‘No Agreement’ letter on March 25, 2019. The protocol was revised and resubmitted for SPA on June 5, 2019. The Division agreed with the revised protocol and issued a “Special Protocol – Agreement” letter on July 18, 2019.

End-of-Phase 2 (EOP2) and Pre-NDA meetings were held on September 20, 2018, and June 26, 2020, respectively.

NDA 214900 for Brexafemme (ibrexafungerp tablets) for oral use was submitted on October 1, 2020, and approved on June 1, 2021, for the treatment of VVC in adult and postmenarchal pediatric females. One of the post marketing requirements was to conduct a study collecting data in women exposed to ibrexafungerp in pregnancy.

A prior approval labeling supplement was submitted on December 15, 2021, to add the information on the PK of ibrexafungerp in postmenarchal pediatric females and in patients with hepatic impairment to *Subsection 12.3 Pharmacokinetics /Special Populations* and to note in *Section 8 Use in Specific Populations* that there is no need for dosage adjustment in patients with mild hepatic impairment. The report from the PK study of ibrexafungerp in adolescent

females included in the supplement fulfilled PMC 4069-3. A Supplement Approval/Fulfillment of Postmarketing Commitment letter was issued on June 15, 2022.

On May 31, 2022, the Applicant submitted a supplemental efficacy application to add the indication of prevention of RVVC in postmenarchal females.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI inspected three clinical sites (Site #160 and Site #156 in the US and Site #458 in Bulgaria) that participated in the phase 3 trial (Study-304), based on the number of enrolled subjects, site-specific efficacy, and inspectional history.

Based on the inspection report, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the proposed indication.

Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records, laboratory reports, and other regulatory documentation; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters. There was no evidence of under-reporting of adverse events. The source records for the primary efficacy endpoint variables related to clinical success (i.e., the investigator's and subject's VSS assessment completed at the Baseline Visit through the Week 24 TOC Visit; concomitant use of additional antifungal therapy; testing to rule out *Neisseria gonorrhoeae*, *Chlamydia trachomatis* or herpes virus; and mycological testing performed by the local and central laboratories) were reviewed and verified against the Applicant's data line listings for all subjects who were randomized at the sites, and no discrepancies were noted.

4.2. Product Quality

Not applicable.

4.3. Clinical Microbiology

Ibrexafungerp is a semi-synthetic triterpenoid derivative which binds to glucan synthase and inhibits the synthesis of β -(1-3)-D-glucan, a component of fungal cell walls. A comprehensive assessment of the clinical microbiology information for ibrexafungerp was provided in the original NDA (see NDA Summary Review dated 6/1/2021).

The single phase 3 study (SCY-078-304 [CANDLE 304]) evaluated the efficacy and safety of oral ibrexafungerp compared to placebo in female subjects 12 years and older with recurrent vulvovaginal candidiasis (RVVC). The phase 3 study design and results are described elsewhere in the review (see Section 8.1). The mMITT population included all randomized women who received at least one dose of trial drug (ibrexafungerp or placebo) who had a confirmed mycological culture for yeast at screening and a negative culture for yeast at baseline (day 1).

- At screening, the majority of women were culture positive (98.5% ibrexafungerp, 100% placebo), with the exception of 2 women that were culture negative. Most women were culture positive for *Candida albicans* (120 who received ibrexafungerp [92.3%], 122 who received placebo [93.8%]). Other *Candida* infections included *C. dublinensis*, *C. fermentati*, *C. glabrata*, *C. guilliermondii*, *C. kefyr*, *C. lusitaniae*, *C. neovariensis*, *C. parapsilosis* and *C. tropicalis*. In addition, 3 subjects presented with *Saccharomyces cerevisiae* at screening. Ten women (6 ibrexafungerp, 4 placebo) were infected with more than one *Candida* spp., of which the most predominant combination was *C. albicans/C. glabrata*. The distribution of *C. albicans* and *C. glabrata* isolates were similar between women from the US compared to ex-US sites; the 4 women infected with *C. dublinensis* were from ex-US sites. Table 1 shows the ibrexafungerp MIC values determined in accordance with Clinical Laboratory and Standards Institute (CLSI) methods. Against *C. albicans* isolates, ibrexafungerp MICs ranged from 0.015 to 0.25 mg/L with a modal value of 0.06 mg/L and MIC_{50/90} values of 0.06 and 0.12 mg/L, respectively. The remaining *Candida* spp. isolates had ibrexafungerp MICs that ranged from 0.25 – 4 mg/L, depending on the species.
- At baseline, after treatment with fluconazole (3 doses) for acute VVC, the majority of women had a negative culture for *Candida* spp. (113 ibrexafungerp subjects [86.9%]; 107 placebo subjects [82.3%]). The remaining women with positive cultures at baseline were 13.1% (17/130) in the ibrexafungerp group and 16.1% (22/130) in the placebo group. Similar to the screening period, the predominant isolates were *C. albicans* followed by *C. glabrata*. The ibrexafungerp MIC values against *C. albicans* ranged from 0.06 to 0.25 mg/L.

Table 1. Ibrexafungerp MIC values against *Candida* spp. isolates in Study SCY-078-304 (mMITT population)

Candida spp. at screening, n (%)	Ibrexafungerp (N = 130)				Placebo (N = 130)			
	N	Range	MIC50	MIC90	N	Range	MIC50	MIC90
At screening								
<i>Candida albicans</i>	120	0.015 - 0.25	0.06	0.12	122	0.015 - 0.25	0.06	0.12
<i>Candida dublinensis</i>	2	0.06 - 0.25	--	--	2	0.12 - 0.5	--	--
<i>Candida fermentati</i>	1	0.25	--	--	0	--	--	--
<i>Candida glabrata</i>	6	0.25 - 1	0.5	1	5	0.25 - 0.5	0.25	0.5

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Candida spp. at screening, n (%)	Ibrexafungerp (N = 130)				Placebo (N = 130)			
	N	Range	MIC50	MIC90	N	Range	MIC50	MIC90
<i>Candida guilliermondii</i>	0	--	--	--	1	2	--	--
<i>Candida kefyr</i>	2	0.06 - 0.25	--	--	0	--	--	--
<i>Candida lusitanae</i>	0	--	--	--	1	4	--	--
<i>Candida nivariensis</i>	1	0.5	--	--	0	--	--	--
<i>Candida parapsilosis</i>	1	0.5	--	--	0	--	--	--
<i>Candida tropicalis</i>	0	--	--	--	1	0.25	--	--
<i>Saccharomyces cerevisiae</i>	1	0.5	--	--	2	1	--	--
At baseline								
<i>Candida albicans</i>	11	0.03 – 0.12	0.06	0.12	19	0.03 – 0.25	0.06	0.12
<i>Candida glabrata</i>	4	0.25 – 0.5	0.5	0.5	3	0.25 – 1	0.25	1
<i>Candida parapsilosis</i>	2	0.25	--	--	0	--	--	--

Source: SCY-078-304 Report Body Table 5-5; Table 14.1.2.4.1

- A comparison of MIC values obtained from paired baseline and post-treatment isolates showed that the majority of the paired isolates had either the same MIC or an MIC that differed by only 1 dilution. Two subjects had post-treatment ibrexafungerp MIC values that were 2 dilutions below the screening MIC and 2 subjects had post-treatment ibrexafungerp MIC values that were 2 dilutions above the screening MIC value. There was no evidence of resistance development; i.e., a 3 to 4-fold increase in MICs.
- At post-treatment visits, several subjects had *Candida* spp. isolates that were different from those identified at screening. The most frequently observed changes occurred on week 12, week 24 and week 36. In the ibrexafungerp group, changes were observed in subjects that were initially infected with *C. albicans* at screening to *C. glabrata* post-treatment, whereas subjects in the placebo group changed from infection with *C. albicans* at screening to *C. kefyr* at one of the post-baseline visits. The clinical significance of this is unknown.
- Overall, the MICs values observed in the study were similar to those reported in surveillance epidemiological studies and in the clinical studies SCY-078-303/SCY-078-306 for the treatment of vulvovaginal candidiasis in adolescents and adult women. There were no differences in the distribution of ibrexafungerp MIC values against *Candida* spp. across treatment groups or geographical areas.

There are no clinical microbiology revisions to Section 12.4 Microbiology of the labeling.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Toxicology findings in the 26-week toxicology study in rats included: clinical signs of labored breathing which correlated with severe phospholipidosis in the form of foamy histiocytes in alveolar tissues, marked irritation and metaplasia in gastric mucosa, and peripheral nerve lesions accompanied by hind-limb paralysis in high-dose animals.

In the stomach mucosa, minimal to marked loss of parietal cells and minimal to moderate accumulation of eosinophilic granules in chief cells occurred in an ibrexafungerp dose-dependent manner. An interpretation of these results by an Expert Panel was that the stomach changes were characteristic of metaplasia and indicative of changes typically associated with a mild reactive response to chemical irritation. The changes were similar to those observed in the 13-week toxicology study in rats but of greater severity in the 26-week study, consistent with a longer duration of ibrexafungerp exposure and prolonged chemical irritation of stomach tissues.

There was a significant increase in the number of foamy histiocytes in alveoli associated with impaired respiration in the 26-week rat study compared to the 13-week rat study. In the 26-week study, marked accumulation of histiocytic cells was described as affecting more than 75% of alveolar tissue with confluent aggregates of foamy histiocytic cells in alveoli and adjacent tissues in lesions consistent with phospholipidosis. Associated findings included perivascular lymphocytic infiltration and alveolar emphysema. Lung histiocytosis and phospholipidosis was also noted in the 13-week study in rats, where the same doses of ibrexafungerp were administered and plasma exposures were similar to those in the 26-week study. However, in the 13-week study, the findings were less severe, suggesting the increased duration of exposure in the 26-week study in rats resulted in more phospholipidosis/histiocytic accumulation in the lung until a toxic severity was achieved. Alveolar histiocytosis was also observed in the 39-week toxicology study in dogs, but impaired respiration was not observed and the histiocytosis resolved after a 12-week recovery period. The less severe presentation of alveolar histiocytosis in dogs may have been influenced by lower exposures, larger lungs, and/or enhanced reversibility in dogs compared to rats.

The study report described peripheral nerve lesions, which occurred in a subset of high-dose male and female rats in the 26-week toxicology study, as minimal focal degeneration of axonal fibers in peripheral nerves in the lumbar spinal cord. The lesions correlated with clinical signs, atrophy of the thigh muscle and hind limb paralysis, in some high-dose animals. Unlike the lung and stomach toxicity, the peripheral neuropathy was not directly linked to severe histiocytosis/phospholipidosis or prolonged chemical irritation. Ibrexafungerp is not expected to enter the brain or CNS tissues, and the mechanism underlying the peripheral neuropathy in rats has not been elucidated. The pathology report for the 26-week study in rats described a

Wallerian type of spontaneous degeneration as an underlying manifestation. Corresponding clinical signs (limited hind limb usage and muscle atrophy) were not reported for the same high dose of ibrexafungerp in rats in the 13-week toxicology study and only occurred after more than 3 months of dosing in the 26-week toxicology study. Like the severe alveolar histiocytosis in the lung and marked changes in the stomach mucosa, the peripheral nerve lesions were influenced by ibrexafungerp dose and dosing duration in the 26-week study in rats. Peripheral nerve lesions and associated clinical signs were not observed in the 13- or 39-week toxicology studies in dogs, but the highest plasma AUC exposures for ibrexafungerp in dogs were approximately half those observed in rats. Ibrexafungerp plasma exposures associated with the planned clinical dose for ibrexafungerp in fed patients are expected to be approximately 10-fold lower than the highest exposures in rats.

The toxicities that occurred in the 26-week toxicology study in rats are not expected to occur with the clinical ibrexafungerp dose and dosing regimen (300 mg approximately 12 hours part for one day, repeated monthly for 6 months) planned for the current sNDA. On the BREXAFEMME product labeling, information regarding the toxicities will be included in Subsection 13.2 which is intended to describe significant animal data necessary for the safe and effective use of drugs in humans that are not incorporated in other labeling sections.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant referenced their original NDA 214900.

5.3. Pharmacology

The safety pharmacology and most of the pharmacokinetic/toxicokinetic studies that were performed with ibrexafungerp were reviewed in the original NDA 214900 review. Major toxicokinetic findings for the 26-week toxicology study in rats and the 39-week toxicology study in dogs are summarized below.

5.4. ADME/PK

Type of Study	Major Findings
TK data from general toxicology studies	
Study Title: A 26-Week Oral Gavage Study Followed by a 12-week Recovery Period in Sprague-Dawley Rat./ Study No.: 1017-2221	Mean plasma TK values for SCY-078 on Day 182 of dosing <u>20 mg/kg/day:</u> C _{max} = 1880 ng/ml in males and 3100 ng/ml in females; AUC _(last) = 35100 ng•hr/ml in males and 55700 ng•hr/ml in females. <u>40 mg/kg/day:</u> C _{max} = 3290 ng/ml in males and 4060 ng/ml in females; AUC _(last) = 73700 ng•hr/ml in males and 87300 ng•hr/ml in females. <u>80 mg/kg/day:</u> C _{max} = 4350 ng/ml in males and 5140 ng/ml in females; AUC _(last) = 94300 ng•hr/ml in males and 107000 ng•hr/ml in females. <u>Accumulation:</u> Day 182 AUC values were approximately 2-fold higher than Day 1 AUC values consistent with plasma accumulation of SCY-078. <u>Dose proportionality:</u> Plasma C _{max} and AUC _(last) values increased approximately dose-proportionately on Day 1, but much less than dose-proportionately on Day 182.

Study Title: SCY-078: 39-Week Oral Gavage Toxicity Study with a 12- Week Recovery Period in Beagle Dogs. / Study No.: 1017-2232	Mean plasma TK values from Day 273 of dosing) <u>30 mg/kg/day:</u> $t_{1/2}$ = 10.50 hours in males and 10.10 hours in females; C_{max} = 1160 ng/ml in males and 1120 ng/ml in females; $AUC_{(last)}$ = 18900 ng•hr/ml in males and 18100 ng•hr/ml in females. <u>60 mg/kg/day:</u> C_{max} = 1510 ng/ml in males and 1770 ng/ml in females; $AUC_{(last)}$ = 23200 ng•hr/ml in males and 25200 ng•hr/ml in females. <u>100 mg/kg/day:</u> C_{max} = 1600 ng/ml in males and 2390 ng/ml in females; $AUC_{(last)}$ = 26700 ng•hr/ml in males and 46100 ng•hr/ml in females. <u>Plasma $t_{1/2}$:</u> On Day 1, $t_{1/2}$ values ranged from 7.44 to 8.42 hours for all sexes and doses. <u>Accumulation:</u> Plasma C_{max} and AUC values tended to increase slightly with the duration of dosing in all the groups with consistently higher values on Day 273 compared to Day 1. <u>Dose proportionality:</u> Overall, plasma C_{max} and AUC values for SCY-078 increased in a less than dose-proportional manner.
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5.5. Toxicology

5.5.1. General Toxicology

No new nonclinical toxicology studies were submitted with the current sNDA. Two chronic toxicology studies, a 26-week study in Sprague-Dawley rats and a 39-week study in Beagle dogs, are considered pivotal in support of the clinical BREXAFEMME dosing schedule described in the current sNDA. The chronic toxicology studies were submitted with the original NDA and the study report for each study is reviewed in full below.

Other toxicology studies for ibrexafungerp, 1-month and 13-week toxicology studies in rats and dogs, genetic toxicology studies, and developmental and reproductive toxicology studies, are reviewed in the original NDA 214900 review.

Study title/ number: A 26-Week Oral Gavage Toxicity Study Followed by a 12-Week Recovery Period in Sprague-Dawley Rats/ 1017-2221

- Toxicity findings primarily occurring in a subset of high-dose males and females included: marked irritation and metaplasia in gastric mucosa, labored breathing correlating with marked phospholipidosis and foamy histiocytes in alveolar tissue, and peripheral nerve degeneration accompanied by hind-limb paralysis and thigh muscle atrophy.

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:

Doses: 0 (vehicle control, Group 1); 20 mg/kg/day (low dose, Group 2); 40 mg/kg/day (mid dose, Group 3); and 80 mg/kg/day (high dose, Group 4) of SCY-078 citrate

Route of administration:	Frequency: once per day Oral gavage
Formulation/Vehicle:	0.5 % (w/v) methyl cellulose in reverse osmosis water
Species/Strain:	Sprague-Dawley Rat
Number/Sex/Group:	Main Study: 20/sex/group. Recovery Study: 5/sex/group. Toxicokinetic Study: 3/sex/group for Group 1 and 9/sex/group for Groups 2-4.
Age:	7-weeks old at the start of dosing.
Satellite groups/ unique design:	Male and female Sprague Dawley rats were administered vehicle or SCY-078 by oral gavage for 26 weeks (182 days) followed by a 12-week recovery period without dosing. Separate toxicokinetic animals were used for toxicokinetic measurements.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings																																													
Mortality	Death or pre-terminal euthanasia for four Main Study animals and two Recovery Study animals occurred in HD animals due to deteriorating clinical condition. While SCY-078-related clinical signs may have contributed to the deaths of three of the animals, two were euthanized with broken bones unrelated to SCY-078 administration. Table 2: Summary of Prematurely Deceased Rats. (Table from the Study Report) <table><tr><th>Dosing Day</th><th>Animal ID</th><th>Dose Level (mg/kg/day)</th><th>Fate</th><th>Probable Cause of Death/Euthanasia</th></tr><tr><td>27</td><td>4515 (Main, high dose female)</td><td>80</td><td>FD</td><td>Stress-related adrenal cortical hypertrophy and aspiration pneumonia</td></tr><tr><td>31</td><td>3013 (Main, mid dose male)</td><td>40</td><td>UE</td><td>Fractured limb</td></tr><tr><td>42</td><td>4020 (Main, high dose male)</td><td>80</td><td>UE</td><td>femoral head fracture and the pelvic dislocation</td></tr><tr><td>115</td><td>1009 (Control, male)</td><td>0</td><td>FD</td><td>Not determined</td></tr><tr><td>138</td><td>4004 (Main, high dose male)</td><td>80</td><td>UE</td><td>Stress-related, adrenal cortical hypertrophy and thymus decreased lymphoid cellularity;</td></tr><tr><td>156</td><td>4012 (Main, high dose male)</td><td>80</td><td>FD</td><td>Pancreatic abscess and peritonitis</td></tr><tr><td>162</td><td>4023 (Recovery, high dose male)</td><td>80</td><td>UE</td><td>Mesenteric lymph node abscess/granuloma and systemic inflammation</td></tr><tr><td>189</td><td>4523 (Recovery, high dose female)</td><td>80</td><td>UE</td><td>Brain tumor (glioma)</td></tr></table> FD – Found Dead; UE – Unscheduled Euthanasia.	Dosing Day	Animal ID	Dose Level (mg/kg/day)	Fate	Probable Cause of Death/Euthanasia	27	4515 (Main, high dose female)	80	FD	Stress-related adrenal cortical hypertrophy and aspiration pneumonia	31	3013 (Main, mid dose male)	40	UE	Fractured limb	42	4020 (Main, high dose male)	80	UE	femoral head fracture and the pelvic dislocation	115	1009 (Control, male)	0	FD	Not determined	138	4004 (Main, high dose male)	80	UE	Stress-related, adrenal cortical hypertrophy and thymus decreased lymphoid cellularity;	156	4012 (Main, high dose male)	80	FD	Pancreatic abscess and peritonitis	162	4023 (Recovery, high dose male)	80	UE	Mesenteric lymph node abscess/granuloma and systemic inflammation	189	4523 (Recovery, high dose female)	80	UE	Brain tumor (glioma)
Dosing Day	Animal ID	Dose Level (mg/kg/day)	Fate	Probable Cause of Death/Euthanasia																																										
27	4515 (Main, high dose female)	80	FD	Stress-related adrenal cortical hypertrophy and aspiration pneumonia																																										
31	3013 (Main, mid dose male)	40	UE	Fractured limb																																										
42	4020 (Main, high dose male)	80	UE	femoral head fracture and the pelvic dislocation																																										
115	1009 (Control, male)	0	FD	Not determined																																										
138	4004 (Main, high dose male)	80	UE	Stress-related, adrenal cortical hypertrophy and thymus decreased lymphoid cellularity;																																										
156	4012 (Main, high dose male)	80	FD	Pancreatic abscess and peritonitis																																										
162	4023 (Recovery, high dose male)	80	UE	Mesenteric lymph node abscess/granuloma and systemic inflammation																																										
189	4523 (Recovery, high dose female)	80	UE	Brain tumor (glioma)																																										
Clinical Signs	Treatment-related clinical signs were noted in males and females at ≥ 20 mg/kg/day. Clinical signs included rales and labored or gasping respiration, head shaking, lack of coordination, severe salivation, limited use of limbs, and muscle atrophy. Signs of abnormal respiration characterized by rales, coughing, wheezing, and/or labored/shallow/ increased respiration were noted rarely in LD and MD animals with a greater incidence and severity in HD animals. The most common respiratory clinical sign, rales, was observed in 2, 11, and 29 animals in the LD, MD, and HD groups respectively. Gasping and labored breathing were respectively observed only in HD animals in 4/25, and 3/25 males and 5/25 and																																													

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	1/25 females. The respiratory effects did not occur every day and generally first occurred after 2 weeks to 1 month of dosing with sporadic repeated incidences for the remaining dosing period and into the recovery period. In HD males and females, there were 6/25 and 4/25 animals with limited hindlimb usage between Weeks 6 and 26 and Weeks 22 to 38 respectively. Two control females were also observed with limited limb usage for a total of 3 days. In the affected animals, limited hindlimb usage was observed beginning 145 days after the initiation of dosing for all animals except one control female (#1506; limited limb usage on Day 84), one MD male (#3013) on Day 31 and two HD males (#4020 on Days 41-42 and #4015 on 6 days from Day 99 – 126). The limited limb usage that was experienced by the MD (#3013) and HD (#4020) males after 31 to 42 days of dosing was due to bone fractures and not considered to be related to SCY-078 administration. Hindlimb muscle atrophy was observed in 3 HD males and 2 HD females beginning on Day 151 near the end of dosing. A histopathology finding at the end of dosing that correlated with limited limb usage and muscle atrophy in a subset of animals was minimal focal degeneration of fibers in the peripheral nerve associated with the lumbar spinal cord. At the end of the recovery period, most of the clinical signs resolved with the exception of limited limb usage and hindlimb muscle atrophy in 1/4 surviving HD females.
Body Weights	Mean body weights were reduced in a SCY-078 dose-dependent manner. Mean body weights were statistically significantly reduced by 6% to 24% in HD males from Day 14 to Day 189, by 7% to 10% in MD males from Day 126 to Day 182, and by 7%-8% in LD males from Day 147 to Day 182. In females, mean body weights were reduced by 6% to 18% and 7% to 24% respectively in the MD and HD groups from Day 14 to Day 189. Mean body weights in LD females tended to be lower than control values throughout dosing, but the differences were not statistically significant. During the recovery period, body weights in all the SCY-078 treatment groups were more similar to control values with no significant differences between groups.
Ophthalmoscopy	No changes in ophthalmoscopy findings were considered related to SCY-078 administration.
Hematology *: $p \leq 0.05$ **: $p \leq 0.01$ ***: $p \leq 0.001$ WBC = white blood cell counts	End of Dosing <u>HD males:</u> +130% WBC***; +549% neutrophils***; +142% percent neutrophils***; +98% monocytes***; +33% percent monocytes*; +21% platelets***; -36% percent lymphocytes***; -82% percent eosinophils*** <u>MD females:</u> +72% percent neutrophils**; +16% platelets*** <u>HD Females:</u> +155% WBC***; +948% neutrophils***; +237% percent neutrophils***; +250% monocytes***; +28% platelets***; -41% percent lymphocytes***; -72% percent eosinophils*** The changes in WBCs may have been related to SCY-078-related histiocytosis. End of Recovery Period: At the end of the recovery period no significant or substantial differences remained compared to control values for all the hematology parameters that were significantly changed relative to control values at the end of dosing consistent with partial or complete reversal.

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Clinical Chemistry *: $p \leq 0.05$ **: $p \leq 0.01$ ***: $p \leq 0.001$ AST = aspartate aminotransferase ALT = alanine aminotransferase ALP = alkaline phosphatase	End of Dosing <u>LD Males:</u> +82% ALT* <u>MD Males:</u> +51% AST***; +74% ALT***; -58% 12-week triglyceride***; -5.5% total protein*; -7.4% albumin*** <u>HD Males:</u> +97% AST***; +117% ALT***; +122% ALP**; -41% cholesterol***; -59% triglyceride***; -7% total protein*; -22% albumin***; -30% albumin/globulin ratio***. <u>MD Females:</u> -67% triglyceride***; -5% total protein* <u>HD Females:</u> +43% AST**; +46% ALT**; +241% ALP***; -30% cholesterol*; -68% triglyceride***; -13% total protein*; -26% albumin***; -32% albumin/globulin ratio***. The increased plasma levels of AST, ALT, and ALP were not considered to be toxicologically relevant because the highest increases did not reach the 300-500% increases that typically signal a concern in nonclinical studies. The changes noted in hepatic enzymes and in cholesterol and triglycerides correlated with hepato-biliary changes including biliary inflammation, Kupffer cell infiltration and single-cell hepatocyte necrosis. The changes noted in albumin and globulin concentration could be compatible with inflammation. End of Recovery Period: After the 12-week recovery period, all the serum chemistry parameters that were significantly changed at the end of dosing occurred with values similar to control values or with only slight differences without reaching statistical significance consistent with partial or complete reversal.
Urinalysis	No changes in urinalysis parameters were considered related to SCY-078 administration.
Gross Pathology	End of Dosing: Gross pathology findings that occurred in a SCY-078 dose-dependent manner for incidence were observed in the lung (irregular surface/raised area in all lobes), spleen (enlarged) and mesenteric and mandibular lymph nodes (enlarged). In the lung, the findings correlated with histiocytosis. Other gross pathology findings that occurred primarily in HD males and females were considered to be possibly related to a bacterial infection (masses in mesentery and thoracic cavity) or stress (enlarged adrenal glands). Small thymus was observed in some animals of both sexes in all groups including the control group and thus was not considered to be directly related to SCY-078 administration. The thymus finding correlated with microscopic detection of lymphoid atrophy and was considered to possibly be related to physiological involution and/or stress. End of the Recovery Period: At the end of the 12-week recovery period, the gross pathology findings observed in MD and HD animals in the Main Study including thoracic and mesenteric masses and findings in the spleen and adrenals were largely reversed. Raised area/pale area/focus in the lung was still apparent in most of the HD males and females at the end of the recovery period, and small thymus remained in one or more recovery animals in most of the control and treatment groups for males and females.
Organ Weights	End of Dosing <u>Adrenal Gland:</u> Adrenal weights (absolute and relative to brain weight) were significantly increased in HD males (43%-47%) and HD females (23%-25%). The increased adrenal weights correlated with enlarged zona fasciculata and may have been related to stress. <u>Ovary:</u> Relative ovary weights (relative to brain weight) were significantly increased approximately 20% compared to control values with no histological correlates. <u>Thymus:</u> Thymus weights (absolute and relative to brain weight) were significantly reduced in MD males (31%), MD females (28%-29%), HD males (36-38%) and HD females (46-47%) compared to control values. The reduced thymus weights were thought to correlate with small thymuses and thymic physiological involution and/or stress. <u>Liver:</u> liver weights (absolute and relative to brain weight) were significantly decreased in MD males (22%-23%) and HD males (20%-22%) with no histological correlates. <u>Pituitary:</u> pituitary weights (absolute and relative to brain weight) were significantly reduced in MD (21%-22%) and HD (29%) females with no histological correlates. <u>Prostate:</u> Prostate weights (absolute and relative to brain weight) were significantly decreased in HD males (20%-22%) compared to control values with no histological correlates.

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	Thyroid/Parathyroid: Thyroid/Parathyroid weights (absolute and relative to brain weight) were significantly decreased in MD males (17%-18%), HD males (24%-25%) and HD females (24%-26%) compared to control values with no histological correlates. End of the Recovery Period: After the 12-week recovery period, no statistically significant changes in any organ weights for the SCY-078 treatment groups occurred for males or females compared to control values. The organ weight increases noted in the spleen and adrenals and the organ weight decreases in pituitary, prostate, and thyroid/parathyroid were no longer present or of substantially less magnitude, suggesting near complete reversal. Relative (to brain weight) ovary weights remained non-significantly elevated by 15% in HD females compared to control values, and liver and thymus weights remained decreased in HD males but not females.
Histopathology Adequate battery: Yes	End of Dosing: Histological changes were observed in the stomach, lung, mesenteric lymph nodes, liver, kidney, pancreas, thymus, and peripheral nerve fibers associated with the lumbar spinal cord. Bacterial Infection: A complicating bacterial infection was reported in the Pathology Report. However, no bacterial stains of the tissue slides were employed to further substantiate and characterize the bacterial infection. According to the report there was complication by secondary bacterial infection with evidence, primarily from the gastrointestinal tract, with abscesses observed most frequently in the mesenteric lymph nodes of 7/17 HD males and 8/19 HD females. Abscesses or lesions related to systemic infection were less frequent in other tissues and organs and included other lymph nodes, lung, spleen, kidney, and abdominal and thoracic cavities. Stomach: In the stomach mucosa, minimal to marked decreases or loss of parietal cells and minimal to moderate accumulation of eosinophilic granules in chief cells occurred in a dose-dependent manner in MD and HD males and females. The gastric mucosa changes were interpreted as metaplasia with the presence of Paneth cells resulting from SCY-078-related irritation of the stomach mucosa. Lung: Dose-dependent phospholipidosis was observed in alveolar tissues in the lung. In HD males and females, markedly severe phospholipidosis was associated with histiocytic inflammation of interstitial alveolar tissue, perivascular lymphocytic infiltration, and alveolar emphysema. Peripheral Spinal Nerves: Minimal focal degeneration of peripheral nerve fibers associated with the lumbar spinal cord was observed with a low incidence in all groups but with a much higher incidence in 8/17 HD males and 7/19 HD females. The lesion was considered to be related to SCY-078 administration and was characterized by focal Wallerian-type degeneration. Correlative findings included minimal atrophy of thigh muscle in approximately 10% of HD males and females and hind limb paralysis in approximately 20% of HD animals. No comparable changes were observed in the sciatic nerves, spinal cord, or the brain. Mesenteric Lymph Nodes: Abscesses or lesions thought to be related to a systemic bacterial infection was observed in 7/17 HD males and 8/19 HD females as well as with a lower incidence in other lymph nodes, lungs, spleen, kidney, and abdominal and thoracic cavities in HD animals. Liver: Liver findings in HD animals included: biliary inflammation, Kupffer cell infiltration, and single-cell necrosis of hepatocytes. Kidney: Brown pigment in renal proximal tubules was observed primarily in HD animals. This finding was considered to likely be an exacerbation of lysosomal lipofuscin accumulations which commonly occur in rats. Pancreas: Minimal acinar cell apoptosis was respectively observed in 6/17 and 8/19 HD males and females. This finding may have been influenced by extensive stomach toxicity in HD animals. Thymus: Decreased lymphoid cellularity in the thymus was observed in most of the male and female animals in all groups including the control group with higher severity in HD animals. This finding was considered to be related to thymic physiological involution and/or stress. End of the Recovery Period: After the 12-week recovery period, histiocytosis/phospholipidosis-related primary lesions were reportedly either fully reversed or as a residual, less severe, presence of minimal to mild lesions in most organs and tissues including the lung, stomach, liver, and kidneys. Degeneration of peripheral nerve fibers occurred with a low incidence in all groups including the control group with no increase in HD animals. Reportedly, substantial recovery was

	also observed with respect to the secondary changes associated with the complicating bacterial infections in various organs. Decreased lymphoid cellularity in the thymus remained with a severity range (mild to marked) similar to that observed at the end of dosing.
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LD: low dose; MD: mid dose; HD: high dose.

-: indicates reduction in parameters compared to control.

Study title/ number: SCY-078: 39-Week Oral Gavage Toxicity Study with a 12-Week Recovery Period in Beagle Dogs/ 1017-2232

- SCY-078 (ibrexafungerp) administration in dogs was associated with sporadic emesis and dose-dependent weight loss. However, no adverse toxicities were observed.
- Prevalent histological findings included phospholipidosis and histiocytosis that was largely reversible in a number of organs including: lung, GI tract, spleen, lymph nodes, thymus, liver, and gall bladder.
- The NOAEL was considered to be the high dose of 100 mg/kg/day which was associated at the end of dosing with plasma C_{max} values for ibrexafungerp of 1600 ng/ml in males and 2390 ng/ml in females and plasma AUC_{last} values of 26700 ng•hr/ml in males and 46100 ng•hr/ml in females.

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	Doses: 0 (vehicle control, Group 1); 30 mg/kg/day (low dose, Group 2); 60 mg/kg/day (mid dose, Group 3); and 100 mg/kg/day (high dose, Group 4) of SCY-078 citrate Frequency: Once per day
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5 % (w/v) methyl cellulose in reverse osmosis water
Species/Strain:	Beagle dogs
Number/Sex/Group:	Main Study: 4/sex/group. Recovery Study: 2/sex/group.
Age:	7-months old at the start of dosing.
Satellite groups/ unique design:	Male and female Beagle dogs were administered SCY-078 citrate (0, 30, 60, and 100 mg/kg/day) dissolved in 0.5% methylcellulose solution once daily for 39 weeks by oral gavage. Main Study animals were euthanized and examined at the end of the 39 weeks of dosing and Recovery Study animals were maintained for an additional 12 weeks without dosing. Toxicokinetic analysis was performed using blood samples obtained from Main Study animals.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	One HD female (Animal No.: 4506) was euthanized humanely on Day 135 (Week 20) due to poor and deteriorating condition. The female first began to demonstrate poor condition (anorexia, dehydration, hypothermia, slightly decreased activity) in Week 1 of dosing. The early effects and the later deterioration were not considered to be clearly related to SCY-078 administration, and a complicating infection was suspected.
Clinical Signs	Daily administration of SCY-078 at ≥ 30 mg/kg/day was associated with reversible signs of sporadic emesis in males and females in conjunction with slight to severe salivation that occurred in a dose-dependent manner throughout the dosing period. There was a greater incidence and/or severity in HD animals compared to LD and MD animals. In males only, signs of thinness and isolated dehydration were also noted. Signs of emesis and thinness correlated with variable, yet reversible lower food intake, and occasional body weight losses or lower body weight gains predominantly at ≥ 60 mg/kg/day. During the recovery period, there was a general resolution of the clinical signs.
Body Weights	Body weight losses were initially noted at Week 1 in MD and HD males and HD females. Thereafter, body weight losses and lower body weight gains were sporadically observed in MD and HD males and females. As a result, mean body weights showed a dose-dependent trend of variable marginal to slight decreases at ≥ 30 mg/kg/day during the dosing period. Statistically significant reductions did not occur in females but occurred in HD males in most weeks beginning in Week 32 until the end of dosing. At the end of dosing, body weights were reduced respectively by 6%, 11%, and 20% in LD, MD, and HD males and by 4%, 8%, and 9% respectively in the same groups in females. When compared to controls, the decrease in body weight in HD males was marginally greater and occurred later in the dosing period peaking at 21% at Week 37. In females, the greatest difference (18%) was noted at Week 11. During the recovery period, body weights were similar in males and females in the control and SCY-078 treatment groups.
Ophthalmoscopy	No SCY-078-related ocular findings were observed.
ECG	No apparent direct or indirect effects of SCY-078 on any of the measured ECG parameters (heart rate, PR interval, QRS duration, QT, and QTc interval measurements) were observed during evaluations in Weeks 13 and 39.
Hematology	No changes in hematology or coagulation parameters were considered to be related to SCY-078 administration in the samples obtained in Weeks 13, 39 (end of dosing), or 51 (end of the recovery period). A non-significant increase in the mean absolute (+99%) and percentage of (+70%) reticulocytes in HD females was observed in Week 13 but not in Week 39 and not on either date in males. The change appeared to be caused by exceptionally high reticulocyte counts in two HD females including one that was prematurely deceased in Week 20. No significant or dose-dependent differences in any of the hematology or coagulation parameters were observed at the end of the recovery period.
Clinical Chemistry	Serum aspartate aminotransferase (AST) was significantly increased in MD and HD males in Weeks 13 and 39 by 47% to 55% respectively and by 29% and 50% in MD and HD females in Week 13 respectively compared to concurrent control levels. However, the increases were of a low magnitude (< 100% increase), did not increase in magnitude with dosing beyond Week 13, and reversed in both males and females after the recovery period.
Urinalysis	No SCY-078-related changes in any of the urinalysis parameters occurred.

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Gross Pathology	SCY-078 administration at 30, 60, and 100 mg/kg/day resulted in SCY-078-related macroscopic dose-dependent changes consisting of pale areas, pale foci, and/or raised areas in the lung correlating with focal to multifocal alveolar accumulation of histiocytic cells. The lung macroscopic findings were not observed in control animals but were observed in 2/4 males and 0/4 females, 1/4 males and 1/4 females, and 3/4 males and 3/4 females in the LD, MD, and HD groups respectively. The lung findings were not present in recovery animals suggesting complete reversal.
Organ Weights	Due to discordant patterns of organ weight changes between the sexes, changed patterns at the end of dosing and at the end of recovery, and the absence of histopathology correlates, the organ weight changes at the end of dosing and at the end of the recovery period were not considered to be toxicologically relevant or clearly related to SCY-078 administration. End of Dosing: At the end of dosing, SCY-078-related changes in mean organ weights occurred for the testes, kidney, liver, thymus, uterus, and spleen in HD males and/or HD females compared to mean control values. However, only the changes in testes weights achieved statistical significance. <u>Testes:</u> Testes weights (absolute and relative to brain weight) were decreased in HD males compared to control values with the change in relative testes weight (-24%) reaching statistical significance. No histological correlates were observed for the decreased testes weights. <u>Kidney:</u> Kidney weights (absolute and relative to brain weight) were non-significantly decreased in MD males (10%-13%), HD males (22%), MD females (14%-19%) and HD females (11%-17%). No histological correlates were observed. <u>Liver:</u> Liver weights (absolute and relative to brain weight) were non-significantly decreased in HD males (21%), but not HD females. No histological correlates were observed <u>Thymus:</u> Thymus weights (absolute and relative to brain weight) were non-significantly decreased in LD males (-23%), MD males (35%-37%), and HD males (32-33%). In contrast, thymus weights were increased by 2% to 96% in females in the LD, MD, and HD groups. <u>Uterus:</u> Uterine weights (absolute and relative to brain weight) were non-significantly increased by 77% to 108% in LD and MD females but non-significantly reduced by 24% to 29% in HD females relative to control values. The uterine increases in the LD and MD females may have been associated with a higher incidence of estrus in these groups. <u>Spleen:</u> Spleen weights (absolute and relative to terminal body weight and brain weight) were non-significantly increased by more than 35% compared to control values in HD males but not in HD females. No histological correlates were observed. End of the Recovery Period: No statistically significant changes in organ weights were observed at the end of the recovery period. However, several patterns of organ weight change occurred, sometimes opposing the changes observed at the end of dosing.

Histopathology Adequate battery: Yes	End of Dosing <u>Lung:</u> In the lung, there was a dose-dependent minimal to mild accumulation of histiocytic cells (aggregates of foamy macrophages) in the alveoli consistent with phospholipidosis. The effects were seen in all three SCY-078 treatment groups but increased for incidence and severity with SCY-078 dose. Unlike the results in the 26-week toxicology study in rats, the aggregates of foamy macrophages in the alveoli of dogs were not associated with impaired respiratory function. <u>GI Tract:</u> In lymphoid tissues in the GI tract, accumulations of histiocytes that were dose-dependent for incidence and severity in SCY-078 treatment groups were observed in gut-associated lymphoid tissues (GALT) in the stomach, cecum, colon, and rectum and Payer's patches in the jejunum and ileum. <u>Lymphoid organs:</u> In the lymphoid system, accumulations of foamy macrophages (consistent with phospholipidosis) were usually dose-dependent for incidence and severity with severity varying from mild to moderate in the spleen, lymph nodes, and thymus. Another finding in the thymus, decreased lymphoid cellularity, correlated with the finding of small thymus and occurred in all groups with similar incidence and severity including the control group for both males and females. Decreased lymphoid cellularity in the thymus did not appear to be related to SCY-078 administration and was considered to be possibly related to stress and physiological involution. <u>Liver and Gall Bladder:</u> Accumulation of histiocytes was observed in all the HD females but not in females in the LD and MD groups or in males in any of the SCY-078 treatment groups. <u>Epididymides:</u> Minimal vacuolation of epithelial cells in the epididymis occurred in a SCY-078 dose-dependent manner for incidence with 2/4, 3/3, and 4/4 males affected in the LD, MD, and HD groups. End of the Recovery Period: After the 12-week recovery period, there was complete reversibility at all doses for histiocytes in the lung, spleen, thymus, liver, and lymph nodes. Residual histiocytes remained in the lymphoid tissues in the GI tract although with lower severity suggesting a trend toward reversibility. Epithelial vacuolation in the epididymides remained with similar severity and decreased lymphoid cellularity in the thymus gland was similar to that observed after the dosing period. The effects in the epididymides and thymus gland, although persistent, were not considered to be adverse.
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LD: low dose; MD: mid dose; HD: high dose.

:- indicates reduction in parameters compared to control.

6 Clinical Pharmacology

6.1. Executive Summary

No new clinical pharmacology studies were submitted with this sNDA. Please refer to the Clinical Pharmacology review associated with the original NDA submission. (NDA 214900 Summary Review dated 6/1/2021).

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The efficacy and safety of ibrexafungerp for reduction in the incidence of RVVC were primarily assessed using the data from a single phase 3 trial (SCY-078-304 or Study-304).

7.2. Efficacy Review Strategy

The efficacy review is based on the randomized portion of Study SCY-078-304. The results presented are based on a review of the clinical study report and analyses conducted on the patient-level data provided in the submission. The sources of data included the Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets which can be found at the following link: <\\CDSESUB1\evsprod\NDA214900\0036\m5\datasets\scy-078-304>.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. SCY-078-304

Trial Design

Study 304 is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of oral ibrexafungerp compared to placebo in female subjects 12 years and older with RVVC. The study consisted of 2 phases: an 'acute phase' where all patients received open-label treatment with fluconazole for a symptomatic episode of VVC and a 'prevention of recurrence phase' where eligible patients were randomized to treatment with ibrexafungerp or placebo. Since a Guidance for Industry specifically for the prevention of recurrence of VCC is not available, the Applicant requested a special protocol assessment during the protocol design phase. Following recommended revisions to the draft, the Division sent the Applicant a "Special Protocol — Agreement" letter on July 18, 2019.

The study was conducted at 49 study sites in Poland (5 sites), Bulgaria (12 sites), Russia (6 sites), and the United States (26 sites). The study started on October 21, 2019 and was completed on November 29, 2021.

Postmenarchal females 12 years (18 years for ex-US sites) and older were eligible for enrollment if they had a diagnosis of symptomatic VVC that met the following criteria at

Screening:

- a) A total composite vulvovaginal signs and symptoms (VSS) score of ≥ 4 . The VSS score is the sum of the rating of each of the signs (edema, erythema and excoriation or fissures) and symptoms (itching, burning and irritation) of infection based on severity (absent = 0; mild = 1; moderate = 2; severe = 3).
- b) A positive microscopic examination with 10% KOH in a vaginal sample collected at Screening revealing yeast forms or budding yeasts
- c) A normal vaginal pH (≤ 4.5)
- d) A minimum of 3 episodes of VVC in the past 12 months, including the current episode, that required treatment with an antifungal. At least 1 of the previous episodes was required to have been a physician-diagnosed episode of VVC with at least 1 positive test confirming vaginal yeast infection (e.g., KOH, culture, or fungal polymerase chain reaction).

Patients who met all eligibility criteria at screening entered the acute phase of the study and received treatment with oral fluconazole 150 mg once a day on Days -14, -11 and -8. At the Baseline Visit (Day 1), subjects who achieved significant resolution of the signs and symptoms of infection following treatment with fluconazole (total composite VSS score ≤ 2), and had culture confirmed VVC from the sample collected at Screening and continued to meet all study eligibility criteria were then eligible for randomization in the Prevention of Recurrence Phase. These women were randomized in a 1:1 ratio to either ibrexafungerp or matching placebo. Treatment was administered as a single day treatment of 2 doses (300 mg ibrexafungerp or matching placebo) given 12 hours apart repeated every 4 weeks for a total of 6 treatments (Day 1, Week 4, Week 8, Week 12, Week 16, and Week 20). Randomization was stratified based on the presence or absence of uncontrolled diabetes mellitus and by geographic region (US or ex-US).

The overall treatment duration of 6 months was chosen based on previous studies that suggest that 6 months of continued suppressive azole therapy may be appropriate for the prevention of RVVC. The approved regimen for the treatment of VVC is two doses of 300 mg ibrexafungerp given 12 hours apart. The studies supporting the treatment indication showed a sustained clinical benefit with high cure rates for up to 25 days (last follow-up). Therefore, a once-every-four-weeks dosing regimen was chosen for the prevention study. Placebo controls are considered acceptable in VVC studies.

During the Prevention of Recurrence Phase, on-site visits occurred on Day 1 and at Weeks 4, 8, 12, 24, and 36 and phone contacts were conducted on Weeks 16, 20, 28, and 32. Unscheduled visits were conducted anytime there were symptoms indicating a potential recurrence or an adverse event. Phone contacts were conducted to check for adverse events, treatment compliance, potential recurrence, and concomitant medication use, including other antifungal agents. Subjects recorded their symptoms of VVC infection on a weekly basis in their diaries and at the time of each visit to the site through the duration of the study. The subject diary was also used to record dosing details, adverse events, and concomitant medication use. A

vulvovaginal exam and rating of signs by the investigator was conducted at the Day 1, Week 12, and Week 24 visits as well as at any visit when a recurrence was suspected. Vaginal samples were collected at the Day 1, Week 12, 24, and 36 visits as well as at any visit when a recurrence was suspected. Quality of Life questionnaires were completed at the Day 1, Week 12, 24, and 36 visits. The Week 24 visit was the test of cure (TOC) visit and Week 36 was the end of follow-up (EOFU) visit.

Note: Subjects enrolled in the study who did not respond to oral fluconazole treatment in the Acute Phase were eligible to enroll in a nested exploratory sub-study, SCY-078-304s. In the nested sub-study, subjects were given one-day oral ibrexafungerp treatment for their unresolved VVC episode. The objective of this exploratory sub-study was to evaluate the efficacy of ibrexafungerp in a population of subjects with a history of RVVC who failed oral fluconazole therapy for the treatment of an acute VVC episode. A total of 24 subjects entered the nested sub-study. Results of this sub-study are not the part of this review.

Study Endpoints

The primary efficacy endpoint was documented clinical success defined as a subject having a TOC evaluation and no mycologically proven, presumed, or suspected recurrence of VVC up to Week 24 (TOC). Mycologically proven recurrence was defined as an episode of VVC with a total composite VSS score ≥ 3 and a culture positive for *Candida* spp. that required antifungal treatment. Presumed recurrence was defined as an episode of VVC with a total composite VSS score ≥ 3 that required antifungal treatment and for which there was a positive KOH test on microscopy but no positive fungal culture. A suspected recurrence was defined as an episode of VVC that required treatment with an antifungal agent (including self-administration with over-the-counter antifungals) regardless of VSS composite score but for which there is no mycological evidence of disease, such as a positive KOH test on microscopy or fungal culture.

The key secondary endpoint was no mycologically proven recurrence at Week 24. Other secondary endpoints included: no mycologically proven recurrence at Week 4, Week 8, Week 12, and Week 36; time to first recurrence of VVC through EOFU; mycological eradication (negative fungal culture) at Week 12, Week 24 and Week 36; no mycologically proven, presumed or suspected recurrences at Week 4, Week 8, Week 12 and Week 36; no mycologically proven or presumed recurrences at Week 4, Week 8, Week 12, Week 24, and Week 36; the number (absolute and categorized at 0, 1, 2 to 3, or ≥ 4) of recurrences (mycologically proven, presumed or suspected) of VVC from Baseline (Day 1) to Week 24 and Week 36; and improvement in QOL outcomes at Week 12, Week 24, and Week 36 as measured by EQ-5D, SF-36 and FSDS.

Statistical Analysis Plan

The statistical analysis plan (SAP) was finalized on January 14, 2022.

Analysis populations

The Intent-to-Treat (ITT) population includes all randomized subjects who received at least one dose of study drug (ibrexafungerp or placebo).

The modified Intent-to-Treat (mITT) population includes all randomized subjects who received at least one dose of study drug (ibrexafungerp or placebo), who had a confirmed mycological culture for yeast at Screening and a negative culture for yeast at Baseline (Day 1).

The Per-Protocol (PP) population includes all mITT subjects who did not have major protocol deviations likely to affect study efficacy and who had available data at the TOC visit. Subjects who discontinued due to a study drug-related AE were classified as failures for the analyses of efficacy under the PP population.

The primary analysis population for efficacy and the focus of this review is the ITT population. The mITT and PP populations were considered supportive.

The Safety Set (SS) includes all randomized subjects who received at least one dose of study drug (ibrexafungerp or placebo) and who had at least one postbaseline evaluation.

Analysis Methods

The primary analysis was a comparison of the proportion of subjects who had documented clinical success up to Week 24 (TOC) in the ibrexafungerp group versus the placebo group. A Cochran-Mantel-Haenszel (CMH) test adjusted for country was conducted to assess the statistical significance of the difference between treatment groups. The p-value, relative risk and 95% confidence interval were calculated. Additionally, the difference in proportions (ibrexafungerp – placebo) and corresponding 95% confidence interval based on the CMH method were presented as requested by the Division.

Reviewer's Comment: *It should be noted that the protocol stated that the CMH test would be adjusted for site. In the SAP, it was revised to country rather than site. Additionally, uncontrolled diabetes status, a randomization stratification factor, was added in the SAP as an adjustment factor. However, due to very few subjects with uncontrolled diabetes, this factor was not considered in the final analyses. These changes are acceptable and do not impact the integrity of the trial.*

Categorical secondary endpoints were analyzed using the same methods as the primary endpoint. For the categorical endpoints (primary and secondary), missing responses were imputed as non-responders (failures, mycological persistence) in the analyses.

The time to event secondary endpoints were analyzed using the Kaplan-Meier method. Subjects who completed the study without experiencing a recurrence of VVC were censored at the last visit date. Subjects who discontinued early without experiencing a recurrence of VVC

were censored at the last available assessment. Subjects who missed any required assessment of potential recurrence were censored at the last available assessment before the first missed assessment if no previous recurrence was experienced. If there was no post-baseline assessment of potential recurrence, subjects were censored at the first dose date of study treatment.

There was no adjustment made to control the type I error for testing of the secondary endpoints. Therefore, results presented in this review for all secondary endpoints are considered descriptive and p-values reported should be interpreted with caution.

Sample Size Calculation

Assuming response rates of 65% and 43% for ibrexafungerp and placebo, respectively; 90% power; and an alpha level of 0.05, approximately 240 subjects randomized at a 1:1 ratio was needed to declare a difference between ibrexafungerp and placebo at Week 24 based on Fisher's Exact test. It was estimated that approximately 320 subjects would need to enroll in the Acute Phase to randomize 240 subjects in the Prevention of Recurrence Phase. Enrollment into the Acute Phase was discontinued when approximately 240 subjects were randomized.

Interim Analysis

No interim analysis was planned or conducted.

Protocol Amendments

A country-specific addendum to the original protocol was made on September 23, 2019, to change the lower age limit from 12 years to 18 years for sites in Russia, Bulgaria, and Poland. This change does not impact the conduct or integrity of the study.

An additional addendum to the protocol was made on July 10, 2020 (US) and August 20, 2020 (Russia/Poland) to allow all subjects who did not respond to fluconazole treatment during the Acute Phase, regardless of screening mycology results, to enter the Nested Sub-study (SCY-078-304s). This change does not affect the conduct or integrity of the main study.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attested that "The study was conducted in accordance with the protocol, the ethical principles established by the Declaration of Helsinki (as amended in Fortaleza, Brazil, October 2013), the International Council for Harmonization (ICH) tripartite guideline E6: Good Clinical Practice (GCP) guidelines, the US Code of Federal Regulations sections that address clinical research studies, applicable European Union regulations, and/or other national and local ethical and legal requirements, as applicable".

Financial Disclosure

The Applicant certified that the clinical investigators had not entered into any financial arrangements whereby the value of the compensation could affect the outcome of the trial (see Appendix 17.2). None of the investigators had a proprietary interest in the product, had significant equity in the Applicant, or had received significant payments of other sorts as defined in 21 CFR part 54.

Patient Disposition

A total of 440 subjects entered the Acute Phase of the study. Of those that successfully completed the Acute Phase, a total of 260 subjects were randomized in the Prevention of Recurrence Phase. All randomized subjects received at least one dose of study medication to which they were randomized. Therefore, the ITT and Safety populations are the same and include 130 ibrexafungerp subjects and 130 placebo subjects. The mITT population included 112 ibrexafungerp subjects and 107 placebo subjects from the ITT population who had a confirmed mycological culture for yeast at Screening and a negative culture for yeast at Baseline. The PP population included 94 ibrexafungerp and 88 placebo subjects.

Table 3: Analysis Populations for Study 304

Analysis Population	Ibrexafungerp N (%)	Placebo N (%)
ITT/Safety	130 (100)	130 (100)
mITT	112 (86.2)	107 (82.3)
Per-protocol	94 (72.3)	88 (67.7)

Source: Table 5-1 of Clinical Study Report

In the ITT population, 120 (92.3%) ibrexafungerp subjects and 115 (88.5%) placebo subjects completed the TOC visit. A total of 12 (9.2%) ibrexafungerp subjects and 16 (12.3%) placebo subjects discontinued the study prior to the EOFU visit. The primary reasons for premature discontinuation from the study were due to withdrawal by subject or lost to follow-up. Subject disposition including the reason for discontinuing the study is summarized in the following table.

Table 4: Subject Disposition in Study 304 (ITT Population)

	Ibrexafungerp (N=130) n (%)	Placebo (N=130) n (%)
Completed TOC Visit	120 (92.3)	115 (88.5)
Completed Study	118 (90.8)	114 (87.7)
Discontinued Study	12 (9.2)	16 (12.3)
Adverse event	0	2 (1.5)
Lost to follow-up	3 (2.3)	5 (3.8)

Physician Decision	2 (1.5)	0
Pregnancy	1 (0.8)	2 (1.5)
Withdrawal by Subject	4 (3.1)	6 (4.6)
Other	2 (1.5)	1 (0.8)

Source: Table 5-1 of Study 304 Clinical Study Report and confirmed by Reviewer using ADSL dataset

Protocol Violations/Deviations

Major protocol deviations in the ITT population are summarized in table below. At least 1 major protocol deviation was reported for 17 (13.1%) ibrexafungerp subjects and 14 (10.8%) placebo subjects. The most commonly reported major protocol deviations were due to study treatment compliance for both study arms. The reported protocol deviations are not expected to have had an impact on safety or efficacy analyses and the overall study results.

Table 5: Major Protocol Deviations in Study 304 (ITT Population)

Category	ibrexafungerp (N=130) n (%)	Placebo (N=130) n (%)
At least 1 major protocol deviation	17 (13.1)	14 (10.8)
Inclusion criteria	5 (3.8)	2 (1.5)
Study treatment randomization	1 (0.8)	0
Study procedures/assessments	1 (0.8)	3 (2.3)
Study treatment admin/dispense	1 (0.8)	0
Study treatment compliance	10 (7.7)	9 (6.9)
Other protocol deviation	2 (1.5)	1 (0.8)

Source: Adapted from Table 5-2 of Study 304 Clinical Study Report

Note: Subjects could have more than one major protocol deviation

Demographic and Other Baseline Characteristics

Table 6 summarizes demographic and baseline characteristics of subjects for the ITT population. There were no significant differences between the treatment groups. The median age was 33 years, and the majority were in the 18 to less than 36 years age group. Although enrollment was open to adolescents in the United States, no subjects less than 18 years were enrolled. Only a single subject, randomized to ibrexafungerp, was 65 years old (or older).

The majority of the subjects were White (90%) and not Hispanic or Latino (91.5%). All Black subjects (8%) and all Hispanic or Latino subjects (8.5%) were from the United States.

Approximately 1/3 of the subjects were from the United States. Russia and Bulgaria each enrolled 28% of the subjects and 12% were from Poland.

The median body mass index was 23.3 kg/m² and the majority of the subjects were classified as normal weight. Most of the subjects who were classified as obese/morbidly obese (31 of 43)

were from the United States as well as half of the subjects classified as overweight (29 of 57).
Less than 2% of subjects had uncontrolled diabetes (defined as hemoglobin A1C levels of $\geq 8\%$).

Table 6: Demographic and Baseline Characteristics in Study 304 (ITT population)

Characteristic	Ibrexafungerp (N=130) n (%)	Placebo (N=130) n (%)	Total (N=260) n (%)
Sex			
Female	130 (100)	130 (100)	260 (100)
Age (years)			
Mean (sd)	34.1 (10.2)	33.7 (9.3)	33.9 (9.8)
Median	33	33	33
Min, Max	18, 65	18, 61	18, 65
18 to 35	76 (58.5)	76 (58.5)	152 (58.5)
36 to 49	46 (35.4)	49 (37.7)	95 (36.5)
50 to 64	7 (5.4)	5 (3.8)	12 (4.6)
≥ 65	1 (0.8)	0	1 (0.4)
Race			
White	120 (92.3)	114 (87.7)	234 (90.0)
Black	9 (6.9)	12 (9.2)	21 (8.1)
Asian	1 (0.8)	1 (0.8)	2 (0.8)
Other	0	3 (2.3)	3 (1.1)
Ethnicity			
Hispanic or Latino	12 (9.2)	10 (7.7)	22 (8.5)
Not Hispanic or Latino	118 (90.8)	120 (92.3)	238 (91.5)
Country			
Bulgaria	37 (28.5)	35 (26.9)	72 (27.7)
Poland	17 (13.1)	14 (10.8)	31 (11.9)
Russia	34 (26.2)	38 (29.2)	72 (27.7)
United States (US)	42 (32.3)	43 (33.1)	85 (32.7)
Region			
Ex-US	88 (67.7)	87 (66.9)	175 (67.3)
US	42 (32.3)	43 (33.1)	85 (32.7)
Body Mass Index (kg/m²)			
Mean (sd)	25.3 (5.9)	24.5 (5.7)	24.9 (5.8)
Median	23.7	22.8	23.3
Min, Max	17.9, 47.5	17.0, 49.2	17.0, 49.2
Underweight (<18.5)	5 (3.8)	5 (3.8)	10 (3.8)
Normal (18.5-<25)	73 (56.2)	77 (59.2)	150 (57.7)
Overweight (25-<30)	25 (19.2)	32 (24.6)	57 (21.9)
Obese (30-<40)	22 (16.9)	13 (10.0)	35 (13.5)
Morbidly obese (≥ 40)	5 (3.8)	3 (2.3)	8 (3.1)
Uncontrolled Diabetes Mellitus			
Yes	2 (1.5)	2 (1.5)	4 (1.5)
No	128 (98.5)	128 (98.5)	256 (98.5)

Source: Reviewer conducted analyses using ADSL and ADBASE datasets

Of note, majority (~60%) patients enrolled at ex-US sites were below or within normal BMI, whereas ~ 80% of patients enrolled in US sites were either overweight, obese, or morbidly obese. The distribution by BMI between treatment arms were similar at both regions. (Table 7).

Table 7 Demographics by BMI Category and Region (Study 304)

	ibrexafungerp (N=42)	Placebo (N=43)	ibrexafungerp (N=88)	Placebo (N=87)
BMI Category kg/m ²)	Region			
	US		EX-US	
Underweight (<18.5)	1	1	4 (4.5)	4 (4.6)
Normal (18.5-<25)	11 (26.2)	12 (27.9)	62 (70.5)	65 (74.7)
Overweight (25-<30)	12 (28.6)	17 (39.5)	13 (14.8)	15 (17.2)
Obese (30-<40)	13 (31.0)	10 (23.3)	9 (10.2)	3 (3.4)
Morbidly Obese (≥40)	5 (11.9)	3 (6.9)	0	0

Safety and ITT Population

Source: ADSL

Table 8 summarizes VVC-associated baseline characteristics of the ITT population. The majority of subjects had 2 (69%) or 3 (28%) prior episodes of VVC in the prior 12 months (not including the episode at screening). Few subjects had 4 or more prior episodes of VVC. At baseline (following treatment with fluconazole), all but 1 subject had a signs and symptoms score of 0 to 2 as required by randomization eligibility criteria. Most subjects had a score of 0 at baseline. Following treatment with fluconazole, the majority of subjects had a negative culture for *Candida* species at baseline (84.6%). Among those who were culture positive at baseline, *C. albicans* was the most frequently cultured species.

Table 8: VVC-associated Baseline Characteristics in Study 304 (ITT population)

Characteristic	ibrexafungerp (N=130) n (%)	Placebo (N=130) n (%)	Total (N=260) n (%)
Number of Acute VVC episodes in past 12 months			
1	1 (0.8)	0	1 (0.4)
2	92 (70.8)	87 (66.9)	179 (68.8)
3	33 (25.4)	39 (30.0)	72 (27.7)
4	3 (2.3)	3 (2.3)	6 (2.3)
5	1 (0.8)	0	1 (0.4)
6	0	1 (0.8)	1 (0.4)
Baseline Signs and Symptoms Score			
0	79 (60.8)	74 (56.9)	153 (58.8)
1	32 (24.6)	32 (24.6)	64 (24.6)
2	19 (14.6)	23 (17.7)	42 (16.2)
3	0	0	0
4	0	1 (0.8)	1 (0.4)
Culture Result at Baseline			

Negative	113 (86.9)	107 (82.3)	220 (84.6)
Positive	17 (13.1)	22 (16.9)	39 (15.0)
<i>Candida albicans</i>	11 (8.5)	19 (14.6)	30 (11.5)
<i>Candida glabrata</i>	4 (3.1)	3 (2.3)	7 (2.7)
<i>Candida parapsilosis</i>	2 (1.5)	0	2 (0.8)

Source: Reviewer conducted analyses using ADFA and ADBASE datasets

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was assessed by the percentage of the number of doses taken divided by the number of planned doses (24 tablets). Overall, the majority of subjects in both treatment arms had between 80%-100% compliance with study medication: 121 (93.1%) ibrexafungerp subjects and 118 (90.8%) placebo subjects.

The use of concomitant medications (non-antifungal) through Week 24 was reported by 104 (80.0%) ibrexafungerp subjects and 95 (73.1%) placebo subjects in the ITT population. The incidence and type of non-antifungal concomitant medications were generally comparable between treatment groups. The most frequently used non-antifungal concomitant medications used were anilides (paracetamol, aspirin, dextromethorphan, phenylephrine, ascorbic acid and codeine: 20.0% in ibrexafungerp arm and 11.5% in placebo arm); propionic acid derivatives (ibuprofen, ketoprofen, and naproxen: 14.6% in ibrexafungerp arm and 16.2% in placebo arm); and fixed combinations of progestogens and estrogens (13.8% in ibrexafungerp arm and 10.8% in placebo arm).

If the subject experienced a recurrence of VVC, rescue antifungal therapy was permitted. Rescue antifungal therapy medication use was lower for the ibrexafungerp group than the placebo group. At or prior to the TOC visit, 31.5% of ibrexafungerp subjects and 41.5% of placebo subjects in the ITT population received rescue antifungal medication at least once. The most frequently used rescue antifungal medication was fluconazole in 34 (26.2%) ibrexafungerp and 47 (36.2%) placebo subjects. After the TOC visit, rescue antifungal medication use was similar for the ibrexafungerp (13.8%) and placebo (15.4%) subjects. Fluconazole was again the most frequently used rescue antifungal medication in 15 (11.5%) ibrexafungerp subjects and 16 (12.3%) placebo subjects.

Table 9: Use of Rescue Medications in Study 304 (ITT Population)

Timing of Rescue Medication	Ibrexafungerp (N=130) n (%)	Placebo (N=130) n (%)
At or prior to TOC	41 (31.5)	54 (41.5)
After TOC	18 (13.8)	20 (15.4)

Source: Table 5-9 Study 304 Clinical Study Report

Efficacy Results – Primary Endpoint

Clinical response at Week 24 (TOC) for the ITT population is summarized in Table 10. Overall, the proportion of subjects who had documented clinical success up to Week 24 was significantly higher for the ibrexafungerp group compared to the placebo group (65.4% vs 53.1%, $p=0.020$). Most subjects in both arms were clinical failures due to having a mycologically proven recurrence. Missing data to determine clinical outcome leading to an imputed recurrence were minimal and balanced for both treatment arms, approximately 5%.

Table 10: Clinical Response at Week 24 (TOC) (ITT Population)

Response	Ibrexafungerp (N=130)	Placebo (N=130)
Clinical Success, n (%)	85 (65.4)	69 (53.1)
Clinical Failure, n (%)	45 (34.6)	61 (46.9)
Mycologically Proven Recurrence	30 (23.1)	47 (36.2)
Presumed Recurrence	7 (5.4)	3 (2.3)
Suspected Recurrence	2 (1.5)	4 (3.1)
Imputed Recurrence	6 (4.6)	7 (5.4)
Relative Risk (95% CI)	1.24 (1.034, 1.486)	
P-value	0.020	
Difference (95% CI)	12.7 (2.2, 23.1)	

Source: Table 6-1 and Table 14.2.1.1.1. ADHOC of Study 304 Clinical Study Report

Note: Relative Risk, p-value, difference in proportion (ibrexafungerp – placebo), and associated 95% confidence intervals (CI) are from a Cochran-Mantel Haenszel test adjusted for country.

Clinical Success at Week 24 (TOC) by geographic region is summarized in Table 11 for the ITT population. The ex-US region is further summarized by country. For both treatment groups, the clinical success rate at Week 24 is lower in subjects from the United States when compared to the ex-US subjects. Of the 13 total subjects with imputed recurrence in the analysis (Table 9), only 2 subjects (1 subject in each treatment arm) were from the ex-US region. The higher number of imputed recurrences for the United States does not explain the lower response rates observed because even if those subjects were not imputed as a recurrence, the clinical success rates would still be much lower than those observed for the ex-US region. Additionally, no baseline or demographic variable that may be influencing the differences in response rates by region was identified from the data collected. In both regions, however, the ibrexafungerp group had a higher rate of clinical success than the placebo group. The difference between treatment groups for each region was similar but the study was not powered to detect differences within region.

Table 11: Clinical Response at Week 24 (TOC) by Geographic Region (ITT Population)

Geographic Region Country	Response	Ibrexafunger p n (%)	Placebo n (%)	Difference (95%CI)
United States		(N=42)	(N=43)	
	Clinical Success	14 (33.3)	10 (23.3)	10.1 (-9.0, 29.1)

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	Clinical Failure	28 (66.7)	33 (76.7)	
	Proven Recurrence	17 (40.5)	25 (58.1)	
	Presumed Recurrence	4 (9.5)	0	
	Suspected Recurrence	2 (4.8)	2 (4.7)	
	Imputed Recurrence	5 (11.9)	6 (14.0)	
ex-United States		(N=88)	(N=87)	
	Clinical Success	71 (80.7)	59 (67.8)	12.9 (0.04, 25.7)
	Clinical Failure	17 (19.3)	28 (32.2)	
	Proven Recurrence	13 (14.8)	22 (25.3)	
	Presumed Recurrence	3 (3.4)	3 (3.4)	
	Suspected Recurrence	0	2 (2.3)	
	Imputed Recurrence	1 (1.1)	1 (1.1)	
		n/N (%)	n/N (%)	
Bulgaria	Clinical Success	30/37 (81.1)	22/35 (62.9)	18.2 (-2.2, 38.6)
Poland	Clinical Success	10/17 (58.8)	8/14 (57.1)	1.7 (-33.2, 36.6)
Russia	Clinical Success	31/34 (91.2)	29/38 (76.3)	14.9 (-1.7, 31.4)

Source: Table 6-4 of Study 304 Clinical Study Report and reviewer conducted analysis using ADEFF dataset.

Clinical Success at Week 24 (TOC) by additional subgroups is summarized for the ITT population in **Table 12**. Interpretation of these results must be made with caution given lack of type 1 error control for multiple analyses and the limited sample size in some of the subgroup categories. The difference between treatment groups in clinical success rates at Week 24 (TOC) were generally comparable for most subgroups and supportive of the overall population. It should be noted that all Black subjects, all not Hispanic/Latino subjects, and most subjects considered obese (including all morbidly obese) were from the United States. However, the small sample sizes of these subgroups limits the ability to draw definitive conclusions regarding any difference or lack thereof.

Table 12: Clinical Response at Week 24 (TOC) by Various Subgroups (ITT Population)

Subgroup	Ibrexafungerp n/N (%)	Placebo n/N (%)	Difference (95% CI)
Race			
White	80/120 (66.7)	64/114 (56.1)	10.5 (-2.0, 22.7)
Black	4/9 (44.4)	4/12 (33.3)	11.1 (-28.9, 48.4)
Asian	1/1 (100)	0/1 (0)	-
Other	-	1/3 (33.3)	-
Age Group (years)			
18 to < 36	45/76 (59.2)	36/76 (47.4)	11.8 (-4.0, 27.1)
36 to < 50	32/46 (69.6)	30/49 (61.2)	8.3 (-10.8, 26.7)
50 to < 65	7/7 (100.0)	3/5 (60.0)	40.0 (-10.3, 73.8)
≥ 65	1/1 (100.0)	-	-
Ethnicity			
Hispanic or Latino	4/12 (33.3)	1/10 (10.0)	23.3 (-13.7, 51.8)
Not Hispanic or Latino	81/118 (68.6)	68/120 (56.7)	12.0 (-0.3, 23.9)
BMI category			
Underweight (<18.5)	3/5 (60.0)	2/5 (40.0)	20.0 (-37.6, 66.1)
Normal (18.5 to < 25)	53/73 (72.6)	47/77 (61.0)	11.6 (-3.6, 26.0)
Overweight (25 to <30)	15/25 (60.0)	13/32 (40.6)	19.4 (-6.8, 42.9)

Obese (30-<40)	10/22 (45.5)	4/13 (30.8)	14.7 (-18.6, 43.6)
Morbidly Obese (≥40)	4/5 (80.0)	3/3 (100.0)	-20.0 (-57.0, 39.9)

Source: Reviewer conducted analysis using ADEFF dataset.

Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoint was no mycologically proven recurrence at Week 24 (TOC). This endpoint is a less inclusive endpoint than the primary endpoint, Clinical Success, where presumed and suspected recurrences were also reasons for clinical failure. Since most subjects in both treatment arms were clinical failures due to having a mycologically proven recurrence (Table 9), the overall conclusions drawn for the key secondary endpoint are similar to the primary endpoint. The results for mycologically proven recurrence are summarized in Table 13.

Table 13: Mycologically Proven Recurrence at Week 24 (TOC) (ITT population)

Response	Ibrexafungerp (N=130)	Placebo (N=130)
No Mycologically Proven Recurrence, n (%)	92 (70.8)	76 (58.5)
Mycologically Proven Recurrence	38 (29.2)	54 (41.5)
Documented Recurrence	30 (23.1)	47 (36.2)
Imputed Recurrence	8 (6.2)	7 (5.4)
Relative Risk (95% CI)	1.22 (1.032, 1.430)	
P-value	0.019	
Difference (95% CI)	12.6 (2.3, 22.9)	

Source: Table 6-8 and Table 14.2.1.4.1ADHOC of Study 304 Clinical Study Report

Note: Relative Risk, p-value, difference in proportion (ibrexafungerp – placebo), and associated 95% confidence intervals (CI) are from a Cochran-Mantel Haenszel test adjusted for country.

Recurrence was assessed through Week 36 (EOFU). The proportion of subjects with no mycologically proven, presumed, or suspected recurrences through Week 36 was nominally significantly higher for the ibrexafungerp group compared to the placebo group (57.7% vs 46.2%, p=0.034). This demonstrates the effect of ibrexafungerp compared to placebo was maintained following the completion of treatment at Week 20. (Table 14).

Table 14: Recurrence through Week 36 (EOFU) (ITT population)

Response	Ibrexafungerp (N=130)	Placebo (N=130)
No Recurrence, n (%)	75 (57.7)	60 (46.2)
Recurrence, n (%)	55 (42.3)	70 (53.8)
Mycologically Proven Recurrence	37 (28.5)	51 (39.2)
Presumed Recurrence	8 (6.2)	5 (3.8)
Suspected Recurrence	4 (3.1)	5 (3.8)
Imputed Recurrence	6 (4.6)	9 (6.9)
Relative Risk (95% CI)	1.26 (1.017, 1.555)	
P-value	0.034	
Difference (95% CI)	11.9 (1.1, 22.6)	

Source: Table 6-9 and Table 14.2.1.3.1.1. ADHOC of Study 304 Clinical Study Report

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Note: Relative Risk, p-value, difference in proportion (ibrexafungerp – placebo), and associated 95% confidence intervals (CI) are from a Cochran-Mantel Haenszel test adjusted for country.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

As mentioned, the study included QOL assessments at baseline, Week 12, Week 24 (TOC), and Week 36 (EOFU). One of the QOL tools was the Female Sexual Distress Scale-Revised (FSDS-R). The FSDS is a validated instrument to measure sexually related personal distress in women for diagnosing female sexual dysfunction (Derogatis et. al., 2002). The FSDS-R was specifically validated for women with hypoactive sexual desire disorder. However, the FSDS-R has not been validated in the context of RVVC.

(b) (4)

8.1.3. Assessment of Efficacy Across Trials

There is only one trial submitted in support of the efficacy of the ibrexafungerp for the prevention of recurrence of VVC, the indication requested by the Applicant.

8.1.4. Integrated Assessment of Effectiveness

As part of the overall development strategy for ibrexafungerp, it was agreed that two phase 3 trials in women with acute VVC and one phase 3 trial in women with RVVC would be sufficient to support the indications of treatment of VVC and prevention of recurrence of VVC. Therefore, the efficacy of ibrexafungerp for the prevention of recurrence of VVC, the indication requested in this sNDA, is based primarily on the pivotal phase 3 trial SCY-078-304. The indication is also supported in part by the two phase 3 trials conducted for the treatment of an acute episode of VVC reviewed under the original NDA submission.

The Applicant followed the Division's guidance regarding the design of Study SCY-078-304 resulting in the Division issuing the Applicant a "Special Protocol – Agreement" letter. The primary endpoint was documented clinical success defined as a subject with no mycologically proven, presumed, or suspected recurrence of VVC up to Week 24 (TOC). The primary efficacy analysis population was the ITT population including all randomized subjects who received at least 1 dose of study drug.

Statistical superiority of ibrexafungerp over placebo was demonstrated in the proportion of subjects with clinical success at Week 24 (TOC) in the ITT population. Most subjects in both treatment arms were considered a clinical failure due to a mycologically proven recurrence which provides the highest level of certainty in the diagnosis of a recurrence in symptomatic subjects.

Higher response rates for both treatment groups were observed for the ex-US region compared to the United States. Based on the data collected, no likely explanation for this difference was found. However, other cultural factors could have influenced response rates in the United States as compared to countries outside the United States. The regional differences in response rates observed are not overly concerning because of the following:

1. The primary analysis adjusts for country and the overall results were statistically significant.
2. A difference in response rates across regions was also observed in the phase 3 trial, SCY-078-306, submitted to support the treatment of acute VVC indication.

The results for clinical success at follow-up (Week 36) were consistent with those observed at TOC (Week 24) indicating a sustained effect up to 4 months after the last dose of treatment at Week 20.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review of this sNDA is based on the phase 3 RVVC study (Study SCY-078-304).

Please note that the safety of a one-day regimen consisting of 2 doses of ibrexafungerp 300 mg (two tablets of 150 mg) has been established previously in two identical randomized, placebo-controlled phase 3 trials (SCY-078-303 and SCY-078-306) that evaluated the safety and efficacy of oral ibrexafungerp in postmenarchal females with VVC where 545 patients with VVC were exposed to the target dose of ibrexafungerp.

Safety analyses for this application are based on the safety population, which was comprised of all patients randomized to the treatment arms and administered at least 1 dose of study drug. The results are summarized for each treatment arm. All analyses represent events that occurred through the TOC visit.

No major data quality or integrity issues were identified that would preclude performing a safety review for this sNDA. A TEAE was defined as ‘any symptom, sign, illness, or experience that developed or worsened in severity and/or frequency after the study drug was started’. The Applicant’s translations of verbatim terms to Medical Dictionary for Regulatory Activities preferred terms for the events reported in Study 304 were reviewed and found to be acceptable. Certain adverse event (AE) terms related to similar symptoms were pooled together. For instance, the preferred terms ‘abdominal pain upper’, ‘abdominal pain lower’, ‘abdominal discomfort’, and ‘abdominal pain’ were pooled as ‘abdominal pain’. The reason for this pooling was that the use of several terms to denote similar types of AEs would risk underestimating their incidence.

8.2.2. Review of the Safety Database

Overall Exposure

The primary safety dataset to support this submission was comprised of 260 female patients enrolled and treated in Study 304. Prior to randomization, all patients initially received a three-day regimen of fluconazole for their symptomatic VVC episode, and responders then were randomized 1:1 in the main trial (prevention of RVVC Phase), to receive either 300 mg ibrexafungerp every 12 hours or matching placebo one day a month, for six consecutive months. The mean treatment duration was 134 days and 133 days for the ibrexafungerp arm and placebo arm, respectively. (Table 16)

Table 16 Ibrexafungerp Exposure in Subjects with RVVC

	Ibrexafungerp (N=130)
Treatment Duration (Days)	
Mean (SD)	134 (28)
Min, Max	1, 156
Duration of Trial Participation (Days)	
Mean (SD)	257 (50)
Min, Max	32, 312
Cumulative Trial Drug Dose (mg)	
Mean (SD)	3428 (603)
Min, Max	600, 3600

Source: Reviewer's Analysis; ADSL data set

Treatment Compliance

Treatment compliance was similar between both treatment arms (95% for the ibrexafungerp arm and 97% for the placebo arm). Most of the patients in both treatment arms (93%, n=121 in the ibrexafungerp arm; and 91%, n=118 in the placebo arm) had treatment compliance rates ranging between 80 to 100%. (Table 17)

Table 17 Treatment Compliance

Treatment Compliance	Ibrexafungerp (N=130)	Placebo (N=130)
n	130	125
Mean (SD)	95 (17)	97 (11)
Treatment Compliance		
<80%	9 (7)	7 (5)
80%-100%	121 (93)	118 (91)

Source: Reviewer's Analysis; ADSL data set

Subject Disposition

The majority of patients in both treatment arms completed the trial. The proportion of patients who prematurely withdrew from the trial for any reason was 9.2% (n=12) in the ibrexafungerp arm compared to 12.3% (n=16) in the placebo arm. The most frequently reported reason for premature discontinuation from the trial in both treatment arms were 'lost to follow-up' and 'withdrawal by subject'. None of the patients in the ibrexafungerp arm discontinued study drug due to an adverse event.

Demographics and Baseline Characteristics of Safety Population (Study-304)

Since the safety population included all patients in the ITT population, the demographics and baseline characteristics of the safety population are discussed in Section 8.1.2 (Table 6).

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

The size of the safety database for ibrexafungerp for the treatment of postmenarchal females with RVVC was discussed with the FDA and was considered adequate. In FDA's Guidance for Industry, Vulvovaginal Candidiasis: Developing Drugs for Treatment²⁰, a specific safety database size is not noted. This guidance focuses only on treatment of acute VVC and does not discuss clinical development programs focused on preventing or reducing the recurrence of VVC. However, since the safety profile of the proposed dose of ibrexafungerp for a single day use²¹ has been well established through the previous approval of ibrexafungerp for the treatment of VVC (original NDA 214900), the FDA agreed with the Applicant's plan to provide additional safety data from a single well-designed phase 3 trial with a proposed sample size (n=130) exposed to a total of 6 single-day treatments over 6 consecutive months (one single day treatment given monthly for 6 months). The safety data generated from this trial, along with supportive data from other trials of ibrexafungerp in the treatment of acute VVC, provide sufficient evidence of the safety of the proposed dosing regimen of ibrexafungerp.

Issues Regarding Data Integrity and Submission Quality

The submission was well organized. Case report forms were reviewed to assess the consistency of the data submitted. The reported terms for adverse events (AEs) matched the MedDRA dictionary terms used during the trial. Clinical inspection of three study sites revealed no evidence of under-reporting of adverse events or other issues related to study conduct. [See subsection 4.1]

Categorization of Adverse Events

Clinical trial data were independently analyzed by the reviewer using JMP software. No major data quality or integrity issues were identified that precluded performing a thorough safety review. No significant issues were identified with respect to recording, coding, and categorizing AEs. All safety analyses represent events that occurred through the TOC visit (i.e., 4 weeks after the last dose of study drug). Treatment emergent adverse events were defined as AEs which

²⁰ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/vulvovaginal-candidiasis-developing-drugs-treatment>

²¹ A single-day treatment consisted of 2 doses of 300 mg each given twice every 12 hours, i.e., a total single-day dose of 600 mg.

started after the first administration of study drug, or clinical conditions which started before the first administration of study drug but worsened after the start of study drug.

8.2.4. Safety Results

Overall, TEAEs were similar between the treatment arms except those that were considered related to the study drug by the investigator. Treatment related TEAEs were approximately twice as high in the ibrexafungerp arm compared to the placebo arm. (Table 18)

Table 18 Safety Summary

Number Of Subjects With	Ibrexafungerp (N=130) n (%)	Placebo (N=130) n (%)
Any TEAE	82 (63.1)	68 (52.3)
Any SAEs	1* (0.8)	0
Any Treatment-Related TEAEs	19 (14.6)	9 (6.9)
Any Treatment-Related SAEs	0	0
TEAE leading to Discontinuation of Treatment	0	3 (2.3)
TEAE leading to Discontinuation from Study	0	2 (1.5)
Any Adverse Event Leading to Death	0	0

Source: Reviewer's Analysis; ADAE data set

Deaths

There were no deaths in Study 304.

Serious Adverse Events

Two patients (1.5%) in the ibrexafungerp arm experienced serious adverse events (SAEs), which were not considered related to study drug. One patient experienced SAEs of COVID-19 pneumonia and influenza (narrative below). These SAEs were considered as severe in intensity, and not related to the study drug by the investigator.

Another patient in the ibrexafungerp arm experienced SAEs of 'adnexa uteri cyst', and 'hemorrhagic ovarian cyst', 6 days after receiving the first dose of fluconazole (on Study Day -7) prior to entering the main RVVC study. The investigator considered these events to be severe in intensity and not related to the treatment (fluconazole). The occurrence of the events was attributed to the patient's underlying condition of ovarian cyst. The adnexa uteri cyst and hemorrhagic ovarian cyst were considered resolved on Study Day -2. The patient entered the main study on Study Day 1 and completed the study successfully.

There were no SAEs experienced by any patients in the placebo arm.

Narrative of Patient with SAEs of COVID-19 Pneumonia and Influenza (b) (6):

The patient was a 29-year-old African American female with a medical history of 3 caesarean sections and 2 episodes of vulvovaginal mycotic infections. The patient entered the main study (prevention of recurrent VVC phase) after completing three 150-mg doses of fluconazole per protocol. No prior medications or concomitant medications were reported at study entry. On Study Day 53, the patient experienced SAEs of COVID-19 pneumonia and influenza and was hospitalized. The investigator considered both the events to be severe in intensity and not related to study drug. No action was taken with the study drug due to these events. Therapeutic measures taken for the treatment of COVID-19 pneumonia and influenza included nasal oxygen. No results of relevant investigations and lab tests were provided, as no medical records were received from the hospital by the Applicant. The events of COVID-19 pneumonia and influenza were considered to be resolved on Study Day 66 and the patient was discharged that day. The patient completed the study successfully without any reported adverse sequelae.

Dropouts and/or Discontinuations Due to Adverse Events

There were no patients in the ibrexafungerp arm who discontinued study treatment or the study due to adverse events. There were three patients in the placebo arm who discontinued the study treatment due to an AE and two of them were also discontinued from the study:

- Patient #1 had TEAEs of 'GGT increased' and 'thrombocytopenia', both were reported as moderate in severity and not related to the study drug (Placebo). These AEs led to treatment dose interruption and discontinuation from the study.
- Patient #2 had a TEAE of 'morning sickness', which was mild and considered not related to study drug (Placebo). The patient's pregnancy test returned positive leading to discontinuation from the study treatment.
- Patient #3 had a TEAE of 'rash' on Study Day 15, which was reported as moderate in severity and related to study treatment (placebo), leading to discontinuation from the treatment and the study. This patient's concomitant medications at study entry included metformin and glibenclamide for type 2 diabetes mellitus. Therapeutic measures for the rash included topical hydrocortisone and oral prednisone. The rash was reported as resolved on Study Day 47.

Significant Adverse Events

None

Treatment Emergent Adverse Events

The most common TEAEs in Study 304 are summarized in Table 19. Out of 260 patients, 82 (63.1%) patients in the ibrexafungerp arm and 68 (52.3%) patients in the placebo arm had at least one TEAE. A total of 19 (14.6%) of subjects in the ibrexafungerp arm experienced treatment related TEAEs as compared to 9(6.9%) subjects in the placebo arm

Overall, the majority of TEAEs were mild to moderate in severity and were reported at a higher frequency in the ibrexafungerp arm compared to the placebo arm. There were 4 patients in the ibrexafungerp arm that reported 'severe' TEAEs of COVID-19 pneumonia with influenza, hypertension, abdominal pain upper, and dysmenorrhea. In the placebo arm, 3 patients reported severe TEAEs of anxiety, depression, diabetes mellitus, and acute otitis media.

The most frequently reported TEAEs were classified as 'Infections and Infestations' (21%, n=27; and 15%, n=19 in the ibrexafungerp and placebo arms, respectively). The most frequently reported TEAE in the Infections and Infestations category was bacterial vaginosis (BV). However, the proportions of patients who had BV were similar between the treatment arms (~8%, n=10 patients in each treatment arm).

Nervous system disorders (preferred term 'headache') was the next most common TEAE, and the incidence was disproportionately higher (18%, n=23) in the ibrexafungerp arm compared to the placebo arm (8%, n=10).

Gastrointestinal (GI) disorders were the next most commonly reported TEAEs (19%, n=24; and 13%, n=17 in the ibrexafungerp and placebo arms, respectively). The most frequently reported TEAEs among the GI disorders were diarrhea, nausea and abdominal pain. (Table 19)

Table 19 Treatment Emergent Adverse Events by System Organ Class (SOC) and by Preferred Terms (PT)

	Ibrexafungerp N=130 n (%)	Placebo N=130 n (%)
Total # of TEAE (events)	253	187
# Subjects with at Least One TEAE	82 (63.1)	68 (52.3)
Infections and infestations	30 (23.1)	24 (18.5)
Bacterial vaginosis	10 (7.7)	11 (8.5)
COVID-19	7 (5.4)	5 (3.8)
Urinary tract infection	5 (3.8)	2 (1.5)
Resp tract Infection	9	7
Vulvovaginal candidiasis	2 (1.5)	3 (2.3)
Nervous system disorders	25 (19.2)	11 (8.5)

Headache	23 (19.2)	11 (8.5)
Gastrointestinal disorders	24 (18.5)	17 (13.1)
Diarrhea	10 (7.7)	5 (3.8)
Nausea	7 (5.4)	5 (3.8)
Abdominal pain	13 (10.0)	9 (6.9)
Toothache	2 (1.5)	3 (2.3)
Reproductive system disorders	6 (4.6)	3 (2.3)
Dysmenorrhea	3 (2.3)	3 (2.3)
Vaginal discharge	3 (2.3)	0
Respiratory, thoracic and mediastinal disorders	5 (3.8)	4 (3.1)
Oropharyngeal pain	5 (3.8)	4 (3.1)
Musculoskeletal and connective tissue disorders	5 (3.8)	4 (3.1)
Myalgia	2 (1.5)	3 (2.3)
Back pain	3 (2.3)	1 (0.8)
General disorders and administration site reactions	4 (3.1)	0
Fatigue	4 (3.1)	0

Source: Reviewer's Analysis; ADAE data set

Note: One subject may have had more than one TEAE.

Common Adverse Drug Reactions

Table 20 summarizes adverse events that were also considered adverse drug reactions (ADRs)²² which occurred at a frequency of >2% of patients on ibrexafungerp. In the RVVC trial headache (HA) occurred at a higher frequency and with a disproportionately high incidence in the ibrexafungerp arm compared to the placebo arm. All HA events resolved without any sequelae. In prior phase 3 trials for VVC, HA occurred in approximately 8% of patients in both treatment arms. The reason for this discrepancy is unclear, and it is uncertain whether the higher incidence of HA in the ibrexafungerp arm in Study 304 trial was associated with the longer duration of administration. Of note, ibrexafungerp does not cross blood brain barrier; therefore, direct CNS toxicity is not expected. Additionally, the proposed dose regimen for RVVC is 6 instances of a single day dosing separated by a month, and the estimated exposure duration for each dosing period is ~ 4 days (i.e., 5 times the half-life of ibrexafungerp of approximately 20 hours). This regimen would result in an intermittent once-a-month exposure of short duration, and it is expected to be cleared entirely from the plasma and tissue

²² An adverse drug reaction (ADR) is an undesirable effect reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

compartment before the next monthly dose is administered. Nevertheless, these AEs will be monitored via routine periodic adverse event reporting.

Interestingly, the TEAE of 'dizziness' was reported in >2% of patients in phase 3 trials for VVC treatment (3.3% ibrexafungerp arm; 2.5% placebo arm), but no patient experienced dizziness in either treatment arm in the RVVC trial (Study 304).

Table 20 Common Adverse Reactions Occurring in $\geq$ 2% of Patients Receiving Ibrexafungerp

Adverse Reaction	Ibrexafungerp N = 130 n (%)	Placebo N = 130 n (%)
Headache	23 (17.6)	10 (7.6)
Abdominal pain*	13 (10.0)	9 (6.9)
Diarrhea	10 (7.7)	5 (3.8)
Nausea	7 (5.4)	5 (3.8)
Urinary tract infections	5 (3.8)	1 (0.8)
Fatigue	4 (3.1)	0

*Includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort
Source: Reviewer's Analysis, ADAE data set

Laboratory Findings

In Study 304, routine laboratory safety testing was performed at baseline and at Week 12 (Day 84 $\pm$ 3 day). Overall, mean hematology and blood chemistry values observed at Week 12 (Day 84) were generally similar to those observed at baseline, with no notable differences between treatment arms. No apparent clinically relevant changes were seen in hematology, blood chemistry, or hepatic parameters. There were few sporadic shifts in blood chemistry values from normal at baseline to low or high after dosing, with no notable differences between the treatment arms. The analysis of shift from baseline values (i.e., from normal or low to high) did not reveal any patterns.

Of note, Study 304 had pre-specified criteria to evaluate events of clinical interest (ECIs) related to transaminase elevations: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 8 x the upper limit of normal (ULN), confirmed by repeat testing; ALT or AST > 5 x ULN for more than 2 weeks or accompanied by total bilirubin > 2 x ULN.

None of the patients in either treatment arm met the above criteria for laboratory abnormalities.

Vital Signs

Physical examinations were conducted at Baseline, Week 12 and Week 24 visits. Vital signs were measured weekly from Baseline to the Week 12 visit, then at Week 24 (TOC visit) and

Week 36 (EOFU visit). Mean vital sign measurements observed at any visits were generally similar to those observed at baseline, with no notable differences between treatment arms.

QT

A thorough QT study was submitted with the original NDA submission in 2021. In summary, at a concentration of 5 times or greater than that achieved after a single day 300 mg twice daily dose, ibrexafungerp did not prolong the QTc interval to any clinically relevant extent.

Immunogenicity

Not applicable

9 Safety Analyses by Demographic Subgroups

Safety analyses by demographic subgroup included the following categories: age group, BMI group, geographic region (USA and ex-USA), race, ethnicity, and baseline disease characteristics, including number of recurrent VVC episodes in the prior year (<4 times, ≥4 times), presence or absence of uncontrolled diabetes mellitus, and severity of VVC at screening through the TOC visit.

Severity of VVC was assessed by conducting two forms of categorization of the composite score of the VSS scale. Category I included VSS scores <7 or ≥7; and Category II included VSS scores of '4 to 7', '8 to 12', and '≥13'.

Please note that the number of patients by subgroups were small and were not powered for inferential statistics. In terms of race, ethnicity and age, the majority of patients were White, non-Hispanic and between 18-36 years of age. There were very few patients in the 50 to 65 year age group and only one patient was >65 years old; thus, meaningful interpretation of AE findings in these age categories was not possible. Of note, in adolescents and geriatric PK studies, there were no clinically significant differences in the PK and safety of ibrexafungerp in adolescent patients (ages 12 to 17 years), or geriatric patients (ages 65 to 76 years). Overall, there were no concerning safety findings identified in the safety analyses by age, race, and ethnicity. (Table 21).

Analysis of TEAEs by geographic region showed a larger difference in incidence of TEAEs between the treatment arms at US sites compared to ex-US sites. However, at both US and ex-US sites, a higher proportion of TEAEs occurred in patients receiving Ibrexafungerp compared to placebo.

Based on BMI categories, patients who were obese or morbidly obese had a numerically higher incidence of TEAEs in the ibrexafungerp arm compared to patients in other BMI categories. However, due to small numbers in each subgroup, findings should be interpreted with caution.

The rates of TEAEs were higher in the ibrexafungerp arm compared to the placebo arm irrespective of baseline disease severity score. (Table 21)

Table 21 Summary of TEAEs by Demographic Subgroups

	Ibrexafungerp N=130 n/Ns (%)	Placebo N=130 n/Ns (%)	Risk Difference (%) (95% CI)
Age group, years, n (%)			
≥18 to <36	44/76 (57.9)	38/76 (50.0)	7.9 (-7.9, 23.7)
≥36 to <50	34/46 (73.9)	30/49 (61.2)	12.7 (-5.9, 31.3)
≥50 to <65	4/7 (57.1)	0/5 (0)	57.1 (20.5, 93.8)
≥65	0/1 (0)	0/0 (NA)	NA
Race, n (%)			
Asian	1/1 (100)	1/1 (100)	0 (0, 0)
Black or African American	6/9 (66.7)	4/12 (33.3)	33.3 (-7.4, 74.1)
Other	0/0 (NA)	2/3 (66.7)	NA
White	75/120 (62.5)	61/114 (53.5)	9.0 (-3.6, 21.6)
Ethnicity, n (%)			
Hispanic or Latino	7/12 (58.3)	4/10 (40.0)	18.3 (-22.9, 59.6)
Not Hispanic or Latino	75/118 (63.6)	64/120 (53.3)	10.2 (-2.2, 22.7)
Body Mass Index, n (%)			
Underweight (<18.5 kg/m ²)	5/5 (100)	3/5 (60.0)	40.0 (-2.9, 82.9)
Normal (18.5 to <25 kg/m ²)	42/73 (57.5)	37/77 (48.1)	9.5 (-6.4, 25.4)
Overweight (25 to <30 kg/m ²)	13/25 (52.0)	19/32 (59.4)	-7.4 (-33.3, 18.6)
Obese (30 to <40 kg/m ²)	17/22 (77.3)	7/13 (53.8)	23.4 (-8.8, 55.7)
Morbidly Obese (≥40 kg/m ²)	5/5 (100)	2/3 (66.7)	33.3 (-20.0, 86.7)
Geographic Region, n (%)			
EX-USA	52/88 (59.1)	44/87 (50.6)	8.5 (-6.2, 23.2)
United States	30/42 (71.4)	24/43 (55.8)	15.6 (-4.6, 35.8)
Number of Recurrent VVC Episodes in Prior Year, n (%)			
<4	78/126 (61.9)	64/126 (50.8)	11.1 (-1.1, 23.3)
≥4	4/4 (100)	4/4 (100)	0 (0, 0)
Severity of VVC at Screening by Composite Score of VSS Scale, n (%)			
<7	12/18 (66.7)	8/16 (50.0)	16.7 (-16.1, 49.4)
≥7	70/112 (62.5)	60/114 (52.6)	9.9 (-3.0, 22.7)
Severity of VVC at Screening by Composite Score of VSS Scale, n (%)			
4 to 7	20/29 (69.0)	17/32 (53.1)	15.8 (-8.3, 40.0)

	Ibrexafungerp N=130 n/N _s (%)	Placebo N=130 n/N _s (%)	Risk Difference (%) (95% CI)
8 to 12	51/77 (66.2)	43/67 (64.2)	2.1 (-13.5, 17.7)
≥13	11/24 (45.8)	8/31 (25.8)	20.0 (-5.2, 45.2)
Uncontrolled Diabetes Mellitus, n (%)			
N	80/128 (62.5)	66/128 (51.6)	10.9 (-1.1, 23.0)
Y	2/2 (100)	2/2 (100)	0 (0, 0)

Source: Reviewer's Analysis

N_s = total number of subjects in the group; VSS= Vulvovaginal Signs and Symptoms Scale.

Note: The signs (edema, erythema, and excoriation or fissures) and symptoms (itching, burning, and irritation) of infection were assessed and rated by the investigator and the subject, respectively, on the VSS scale (provided in Protocol Section 21.2 [Appendix B]). The VSS scale is a standardized, predefined scale where each sign and symptom were given a numerical rating based on severity (absent = 0; mild = 1; moderate = 2; severe = 3) to calculate a total composite VSS score. The symptoms of infection were rated by the subject on a weekly basis and at the time of each scheduled or unscheduled visit to the site throughout the Prevention of Recurrence Phase. Vaginal examinations were conducted by the investigator to rate the subject's signs of infection at protocol-specified visits and anytime that there was suspicion of a potential recurrence.

Overall, there was a higher incidence of TEAEs by demographic subgroups and baseline characteristics in the ibrexafungerp arm compared to placebo.

9.1.1. Safety in Special groups/Populations

Pregnancy

Nonclinical Experience

Ibrexafungerp was associated with serious dose-related fetal malformations in rabbits at exposures 5- to 13-times the expected clinical exposure.

In an embryo-fetal study in rabbits, no fetal malformations or variations were observed with the 10 mg/kg/day dose of ibrexafungerp (~ 2 times the maximum recommended human dose (MHRD) based on AUC comparison). However, in the mid-dose group administered 25 mg/kg/day of ibrexafungerp (~ 5 times MHRD), fetal malformations including absent ear pinna, general body craniorachischisis, trunk kyphosis, absent hind paw, and forelimb phocomelia occurred in a single fetus but not in fetuses in the vehicle control group or in comparable historical control data. In the high dose group of 50 mg/kg/day (~ 13 MHRD), malformations including absent hind paw and anencephaly occurred with an increased litter incidence as well as other malformations that occurred in single fetuses (including absent ear pinna, forelimb phocomelia, and absent thyroid gland), but not in comparable historical control data.

In contrast to the results of the embryo-fetal study in rabbits, ibrexafungerp was not associated with fetal malformations in a rat embryo-fetal study. There were no fetal malformations seen at up to the high dose of 50 mg/kg/day ibrexafungerp (~ 5 times MHRD). Ibrexafungerp did not

inhibit male or female fertility in a fertility study in rats or produce adverse effects on the survival, growth, behavior, or reproductive ability of first-generation offspring in a pre-postnatal study in rats.

Human Experience

There are limited data on ibrexafungerp use in pregnant women to evaluate for drug-associated risks of birth defects, miscarriages, or adverse maternal or fetal outcomes. All patients enrolled in Study 304 had a negative pregnancy test at the screening visit and were to follow a medically acceptable contraceptive method during study participation. Pregnancy was reported for 4 patients in this trial (1 patient who received 3 daily treatments with ibrexafungerp, 2 patients who received placebo and in 1 patient prior to randomization to the double-blind treatment). One pregnancy in the placebo arm was electively terminated and the other 3 reported normal delivery of a healthy newborn.

There is a planned post-marketing required pregnancy safety study (PMR-4069-1) in females exposed to ibrexafungerp. The goal of the study is to provide clinically relevant human safety data that can inform health care providers treating or counseling patients who are pregnant or anticipating pregnancy about the safety of ibrexafungerp through inclusion of the information in the prescribing information.²³

Addition of Box Warning:

Ibrexafungerp is anticipated to be used by females of reproductive potential and for the indication of RVVC it will be used as intermittent, single day dosing once a month for six months. Therefore, the risk of inadvertent exposure during pregnancy is increased compared to the acute VVC treatment indication. Thus, a boxed warning is added to the PI to mitigate the risk of a serious adverse reaction of fetal harm by increasing the visibility of the warning to providers.

Lactation

There is no information on the presence of ibrexafungerp in human milk, the effects on the breast-fed infant, or the effects on milk production.

There is a post marketing requirement for a milk-only clinical lactation study of ibrexafungerp in females of reproductive potential (PMR-4069-2). The clinical lactation study will assess the amount of drug present in human milk to better inform recommendations for use of ibrexafungerp in lactating women.

²³ <https://www.fda.gov/media/124746/download>

Geriatric Patients

The pharmacokinetics of ibrexafungerp were not altered in geriatric patients (ages 65 to 76 years).

Renal Impairment

The effect of renal impairment on the pharmacokinetics of ibrexafungerp has not been studied. However, ibrexafungerp is eliminated primarily via metabolism and biliary excretion with renal excretion accounting for <2% of the ibrexafungerp dose. The elimination half-life is ~ 20 hours.

Hepatic Impairment

The effect of mild and moderate hepatic impairment on the pharmacokinetics of ibrexafungerp was studied, and no dosage adjustment of ibrexafungerp is recommended in patients with mild hepatic impairment (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B). Administration in patients with severe hepatic impairment (Child-Pugh Class C) has not been studied.

9.1.2. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Carcinogenesis

Two-year carcinogenicity studies of ibrexafungerp have not been performed because the cumulative exposure of the drug is less than 6 months (24 days total) based on once monthly administration and a short half-life.

Mutagenesis

No mutagenic or clastogenic effects were detected in an in vitro bacterial reverse mutation assay, an in vitro chromosomal aberration assay, and an in vivo bone marrow micronucleus assay in rats.

Impairment of Fertility

In a male and female fertility study in rats, ibrexafungerp was administered to male rats by oral gavage in doses of 10, 20, 40, and 80 mg/kg/day for 28 days before mating and throughout mating and to female rats for 15 days before mating, during mating, and until gestation day (GD) 6. Ibrexafungerp did not impair fertility in either sex at any dose up to the highest dose of 80 mg/kg/day (~10 times the recommended human dose or RHD based on AUC comparison).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

To date, there have been no reports of overdose with ibrexafungerp.

9.1.3. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Ibrexafungerp 150 mg oral tablet was approved in the US in June 2021 for the treatment of VVC at 300 mg every 12 hours for 1 day. Post-authorization safety data are continually monitored by the Applicant (SCYNEXIS) via routine pharmacovigilance. The safety database contains cases of adverse events reported spontaneously to SCYNEXIS, cases reported by the Health Authorities, cases published in the medical literature, cases from SCYNEXIS-sponsored marketing programs, non-interventional studies, and cases of serious AEs reported from clinical studies regardless of causality assessment.

A total of 49 cases of adverse events were reported between December 2021 to August 2022. All cases were non-serious and were reported in the US.

Serious AE and AE with Fatal Outcome

There were no cases with a fatal outcome submitted during this reporting period.

Drug Exposure During Pregnancy or Lactation

There were no cases of drug exposure during pregnancy. One spontaneous report of 'maternal exposure during breast feeding' was listed, however no further details was available for that case.

An information request was also sent to the Applicant on 9/19/2022 to enquire about any case reports of potential exposure during pregnancy. The sponsor replied that there have been no known ibrexafungerp exposures during pregnancy.

Non-serious AEs by System Organ Classification

Table 22 summarizes non-serious adverse events reported between December 2021 through August 2022. Review of post-authorization adverse events data has not revealed any novel safety concerns. Most reported AEs were diarrhea, abdominal pain, and vomiting which are already listed in the prescribing information.

Table 22 Summary of adverse events reported post marketing through August 31, 2022

System Organ Class (SOC) Preferred Term	Adverse Events	
	Total Events	Total Cases
Gastrointestinal disorders	23	23
Abdominal pain	3	3
Abdominal pain upper	2	2
Diarrhea	8	8
Nausea	6	6
Vomiting	4	4

General disorders and administration site conditions	17	17
Drug ineffective/ Therapeutic product effect incomplete	14	14
Malaise/ Fatigue	3	3
Nervous system disorders	3	3
Dizziness/Cold sweats	3	3
Immune system disorders	2	2
Hypersensitivity/ Urticaria	2	2
Injury, poisoning and procedural complications	3	3
Off label use	3	3
Skin and subcutaneous tissue disorders	1	1
Urticaria	1	1
Total	49	49

Source: Sponsor's submitted Post market safety reports

9.1.4. Integrated Assessment of Safety

The safety of oral Ibrexafungerp in post menarchal female patients with RVVC was evaluated in a single phase 3, randomized, multicenter, double-blind, placebo-controlled trial (Study 304). The study evaluated 2 doses of ibrexafungerp 300 mg (two tablets of 150 mg) administered 12 hours apart once monthly for a total of 6 months. The safety profile of the same dose of ibrexafungerp administered for a single day has been established in two randomized phase 3 trials for the treatment of VVC plus additional safety data from multiple phase 1 and 2 trials which provided support for approval of ibrexafungerp for treatment of VVC in postmenarchal females (NDA 214900).

In the phase 3 RVVC trial there were no deaths in either treatment arm. Two patients (1.5%) in the ibrexafungerp arm experienced SAEs (one patient had 'Covid-19 pneumonia' and 'influenza'; and another patient experienced an SAE of 'adnexa uteri cyst'). These SAEs were considered not related to study treatment and resolved without sequelae.

Treatment emergent adverse events were reported by 63.1% (n=82) of patients in the ibrexafungerp arm and 52.3% (n=68) of patients in the placebo arm. Overall, the majority of TEAEs were mild to moderate in severity and were reported at a higher frequency in the ibrexafungerp arm compared to the placebo arm.

The most common adverse drug reactions (incidence $\geq 2\%$) observed with ibrexafungerp treatment were headache (17.6%), abdominal pain (10%), diarrhea (10%), nausea (5.4%), urinary tract infections (3.8%), and fatigue (3.1%). The majority of these adverse reactions were mild to moderate in intensity and resolved within 1-3 days without any sequelae.

The safety data from the phase 3 trial in RVVC are consistent with previously observed adverse events reported in two phase 3 VVC trials, except for the TEAE of headache. In the VVC trials

headache occurred in ~ 8% of patients in both the ibrexafungerp and placebo arms. In the RVVC trial headache was reported at a higher frequency (~18%) and occurred at a higher incidence in patients who received ibrexafungerp compared to the placebo.

There were no new safety signals noted in the RVVC trial. Although there were no patients younger than 18 years old in this trial, additional safety assessments of ibrexafungerp in postmenarchal adolescent (12-17 years old) females are not deemed necessary since the course of the disease and pharmacokinetics of ibrexafungerp in adolescent females are similar to those in adults. To note, recurrent VVC is exceedingly rare in the adolescent age group.

There was a previously recognized safety issue related to fetal malformations observed in one species (rabbits) in an animal study at a dose resulting in exposures 5 to 13 times higher than exposures at the recommended clinical dose. The prescribing Information for ibrexafungerp includes a warning and contraindication for use in pregnancy and includes a statement to assess for pregnancy status prior to administering ibrexafungerp.

For the RVVC indication, since ibrexafungerp will be given as intermittent single day dosing once a month for six months and is anticipated to be used in females of reproductive potential, the risk of inadvertent exposure to ibrexafungerp during pregnancy is increased. Therefore, a boxed warning is added to mitigate the risk of a serious adverse reaction of fetal harm by increasing the visibility of the warning to providers.

9.2. Statistical Issues

There are no major statistical issues.

9.3. Conclusions and Recommendations

Results from the phase 3 trial in patients with RVVC support the approval of ibrexafungerp for use in the treatment of postmenarchal females for reduction in incidence of recurrent VVC and this is also supported by the available clinical evidence from previous approval for the treatment of VVC. No new safety concerns related to the use of ibrexafungerp in females receiving treatment for RVVC were identified in the trial.

10 Advisory Committee Meeting and Other External Consultations

This application was not presented to the Antimicrobial Drugs Advisory Committee or any other external consultants because the application did not raise efficacy or safety issues requiring advisory committee input for the recommended indication.

11 Pediatrics

Ibrexafungerp was approved for treatment of VVC in postmenarchal pediatric females based on extrapolation of efficacy from adequate and well controlled trials of ibrexafungerp in adults with additional data from a study evaluating ibrexafungerp PK and safety in postmenarchal females.

Safety and Efficacy in Pediatric Patients <12 Years Old

The Applicant is seeking an indication for oral ibrexafungerp tablets in postmenarchal females for prevention of RVVC and had requested a partial waiver of pediatric assessments for children less than 12 years old. A partial waiver for the treatment of VVC and prevention of recurrent VVC was granted based on the pathogenesis and epidemiology of VVC, since the disease is rare in pre-pubertal girls. In published studies evaluating vaginal fluid cultures from pediatric patients, *Candida* species were rarely isolated in cultures obtained from pre-pubertal girls.^{24, 25, 26} These findings supported the Applicant's request for a waiver of pediatric assessments in younger children since antifungal therapies such as ibrexafungerp would not be required to treat recurrent vulvovaginitis in this population under most circumstances.

Safety and Efficacy Data in Pediatric Female Patients 12 to 17 Years Old

The phase 3 trial (Study 304) to evaluate the safety and efficacy of ibrexafungerp for the indication of reduction of the incidence of RVVC planned to enroll patients 12 years and older. However, despite the Applicant's attempts, no patient less than 18 years old was enrolled in the trial. The Applicant completed a PK study in 12 to 17-year-old adolescents that did not find any difference in PK between adults and adolescent patients. Safety findings in the PK study were similar to those observed in adults.

Similar to treatment of VVC, the efficacy of ibrexafungerp for reduction of the incidence of RVVC can be extrapolated from the adequate and well-controlled trials conducted in the adult population.

²⁴ Jaquier, A., et al. (1999). "Vulvovaginitis: clinical features, aetiology, and microbiology of the genital tract." Arch Dis Child 81(1): 64-67.

²⁵ Yilmaz, A. E., et al. (2012). "Comparison of clinical and microbiological features of vulvovaginitis in prepubertal and pubertal girls." J Formos Med Assoc 111(7): 392-396.

²⁶ Banerjee, K., et al. (2004). "Low prevalence of genital candidiasis in children." Eur J Clin Microbiol Infect Dis 23(9): 696-698.

12 Labeling Recommendations

12.1. Prescribing Information

This Prescribing Information (PI) review includes a high-level summary of the major changes made to the PI submitted by the Applicant on May 31, 2022. Several sections of the PI were revised during this review cycle. Table 23 below summarizes some key changes including reasons for changes.

Table 23 Summary of Key Changes to the Prescribing Information (recent changes in ‘blue ink’)

Section of the PI	Applicant’s Proposed Text	Revised Text and Rationale for Changes
HIGHLIGHTS (HL) OF PRESCRIBING INFORMATION BOXED WARNING		Addition of BOXED WARNING: WARNING: RISK OF EMBRYO-FETAL TOXICITY <i>See full prescribing information for the complete boxed warning.</i> • BREXAFEMME is contraindicated in pregnancy because it may cause fetal harm based on findings from animal reproductive studies. (4, 5.1) • For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment. Reassessing pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC). (2.3, 5.1) • Advise females of reproductive potential to use effective contraception during treatment of vulvovaginal candidiasis (VVC) and throughout
Reviewer’s Comments: A boxed warning has been added to mitigate the risk of a serious adverse reaction of fetal harm that can be prevented by avoiding use in pregnancy, since the risk of inadvertent exposure to ibrexafungerp during pregnancy is increased with the addition of the new indication for reduction in the incidence of RVVC given the prolonged duration of therapy, intermittent dosing, and anticipated use in females of reproductive potential. In addition, the severity of the potential adverse reaction is serious in proportion to the benefit of using the drug for RVVC during pregnancy. See Section 1.3 Benefit-Risk Assessment for details. The Division will recommend that the Applicant distribute a Dear Health Care Provider (DHCP) letter and referred the Applicant to the FDA Guidance for ‘Dear Health Care Provider (DHCP) Letters’: Improving Communication of Important Safety Information: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/dear-health-care-provider-letters-improving-communication-important-safety-information. Refer to Section 9.1.1 for additional details.		

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ADVERSE REACTIONS	The most frequent adverse reactions (≥ 2%) reported (b) (4) (b) (4) were diarrhea, nausea, abdominal pain, dizziness, and vomiting. (6.1)	<u>Treatment of VVC:</u> The most frequent adverse reactions (incidence ≥ 2%) reported were diarrhea, nausea, abdominal pain, dizziness and vomiting. (6.1) <u>Reduction in the incidence of RVVC:</u> The most frequent adverse reactions (incidence ≥ 2%) reported were headache, abdominal pain, diarrhea, nausea, urinary tract infection and fatigue. (6.1)
Reviewer's Comments: The adverse reactions section of the labeling highlight is updated with addition of most frequent adverse reactions observed in the RVVC trial.		
The remainder of the HL and the TABLE OF CONTENTS (TOC) sections of the PI were revised for consistency with the FULL PRESCRIBING INFORMATION (FPI).		
FULL PRESCRIBING INFORMATION (FPI)		
Section: 1 INDICATIONS AND USAGE	Prevention of recurrent VVC (RVVC) (1.1)	Reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC) (1.1)
Reviewer's Comments: This sentence is rephrased. The Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format Guidance for Industry (July 2018) states that if the indication for a drug is to reduce the risk of the occurrence of a particular clinical outcome, phrases such as “reduce the risk of” or “reduce the incidence of” should be considered rather than using “prevent” in the indication. The use of a term such as prevent may imply a guarantee of success that is not supported by the data. Refer to Section 8.1.4 for additional details.		
Section: 2 DOSAGE AND ADMINISTRATION	2.3 Pregnancy Evaluation Prior to Initiating Treatment Verify the pregnancy status in females of reproductive potential prior to initiating treatment with BREXAFEMME [see Contraindications (4), Warning and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)].	2.3 Pregnancy Evaluation Prior to Initiating Treatment For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment with BREXAFEMME. Reassessment of pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the incidence of RVVC [see Contraindications (4), Warning and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)].
Reviewer's Comments: For additional clarity, revised language was proposed to make it clearer that ibrexafungerp should not be used if pregnant (rather than just verify pregnancy status). Similar edits were added to subsection 5.1 and 8.3 of the FPI. Refer to the Division of Pediatrics and Maternal Health (DPMH) review for additional details.		
Section: 5 WARNINGS AND PRECAUTIONS	Risk of Fetal Toxicity: Based on findings from animal studies, BREXAFEMME use is contraindicated in pregnancy because it may cause fetal harm. In animal reproduction studies, ibrexafungerp administered orally to pregnant rabbits during organogenesis was associated with fetal malformations including absent forelimb(s), absent hindpaw, absent ear pinna, and thoracogastroschisis at dose	Risk of Fetal Toxicity: Based on findings from animal studies, BREXAFEMME use is contraindicated in pregnancy because it may cause fetal harm. In animal reproduction studies, ibrexafungerp administered orally to pregnant rabbits during organogenesis was associated with fetal malformations including absent forelimb(s), absent hindpaw, absent ear pinna, and thoracogastroschisis at dose exposures greater or equal to approximately 5 times the human exposure at the recommended human dose (RHD).

	exposures greater or equal to approximately 5 times the human exposure at the recommended human dose (RHD). Prior to initiating treatment with BREXAFEMME, verify the pregnancy status in females of reproductive potential. Advise females of reproductive potential to use effective contraception during treatment with BREXAFEMME and for 4 days after the last dose [see Use in Specific Populations (8.1, 8.3)].	For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment with BREXAFEMME. Reassessment of pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the incidence of RVVC. Advise females of reproductive potential to use effective contraception during treatment of VVC and throughout the 6-month treatment period for reduction in the incidence of RVVC with BREXAFEMME and, for 4 days after the last dose [see Use in Specific Populations (8.1, 8.3)].																																										
Reviewer's Comments: The sentence is rephrased for clarity.																																												
Section: 6 ADVERSE REACTIONS Subsection 6.1 Clinical Trials Experience (FPI)	Subsection 6.1: Clinical Trials Experience <table border="1"> <caption>Table 2. Adverse Reactions with Rates ≥2% in BREXAFEMME-Treated Patients</caption> <thead> <tr> <th>Adverse Reaction</th><th>BREXAFEMME N = 130 n (%)</th><th>Placebo N = 130 n (%)</th></tr> </thead> <tbody> <tr> <td>Abdominal pain¹</td><td>13 (10.0%)</td><td>9 (6.9%)</td></tr> <tr> <td>Diarrhea</td><td>10 (7.7%)</td><td>5 (3.8%)</td></tr> <tr> <td>Headache²</td><td></td><td>(b) (4)</td></tr> <tr> <td>Nausea</td><td>7 (5.4%)</td><td>5 (3.8%)</td></tr> <tr> <td>Urinary tract infection</td><td>5 (3.8%)</td><td>1 (0.8%)</td></tr> <tr> <td>Fatigue</td><td>4 (3.1%)</td><td>0</td></tr> </tbody> </table> ¹ Includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort (b) (4)	Adverse Reaction	BREXAFEMME N = 130 n (%)	Placebo N = 130 n (%)	Abdominal pain ¹	13 (10.0%)	9 (6.9%)	Diarrhea	10 (7.7%)	5 (3.8%)	Headache ²		(b) (4)	Nausea	7 (5.4%)	5 (3.8%)	Urinary tract infection	5 (3.8%)	1 (0.8%)	Fatigue	4 (3.1%)	0	Subsection 6.1: Clinical Trials Experience <table border="1"> <caption>Table 2. Adverse Reactions with Rates ≥2% in BREXAFEMME-Treated Patients</caption> <thead> <tr> <th>Adverse Reaction¹</th><th>BREXAFEMME N = 130 n (%)</th><th>Placebo N = 130 n (%)</th></tr> </thead> <tbody> <tr> <td>Headache</td><td>23 (17.6)</td><td>10 (7.6)</td></tr> <tr> <td>Abdominal pain²</td><td>13 (10.0)</td><td>9 (6.9)</td></tr> <tr> <td>Diarrhea</td><td>10 (7.7)</td><td>5 (3.8)</td></tr> <tr> <td>Nausea</td><td>7 (5.4)</td><td>5 (3.8)</td></tr> <tr> <td>Urinary tract infection</td><td>5 (3.8)</td><td>1 (0.8)</td></tr> <tr> <td>Fatigue</td><td>4 (3.1)</td><td>0</td></tr> </tbody> </table> ¹ A single patient may have had multiple instances of adverse reactions. Only one episode of adverse reaction is counted per patient. ² Includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort	Adverse Reaction ¹	BREXAFEMME N = 130 n (%)	Placebo N = 130 n (%)	Headache	23 (17.6)	10 (7.6)	Abdominal pain ²	13 (10.0)	9 (6.9)	Diarrhea	10 (7.7)	5 (3.8)	Nausea	7 (5.4)	5 (3.8)	Urinary tract infection	5 (3.8)	1 (0.8)	Fatigue	4 (3.1)	0
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Reviewer's Comments: Adverse reactions (ARs) are updated, proportions corrected, and the AR of 'headache' is moved up based on the frequency of occurrence in the RVVC trial. (b) (4) Patients received 6 sequential doses 30 days apart in the RVVC trial, thus headaches occurring within the 180-day treatment period are included similar to other reported ARs. Furthermore, the incidence of headache was disproportionately higher in the ibrexafungerp arm compared to placebo. Only one episode of headache per subject during treatment period is included in this table.																																												
Section: 8 USE IN SPECIFIC POPULATIONS	8.3 Females and Males of Reproductive Potential <u>Contraception</u> <i>Females</i> Advise females of reproductive potential to use effective contraception during treatment with BREXAFEMME and for 4 days after the last dose.	8.3 Females and Males of Reproductive Potential <u>Contraception</u> <i>Females</i> For treatment of VVC, advise females of reproductive potential to use effective contraception during treatment with BREXAFEMME and for 4 days after the last dose. For reduction in the incidence of RVVC, advise females of reproductive potential to use effective																																										

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		contraception throughout the 6-month treatment period with BREXAFEMME and for 4 days after the last dose.
Section: 13 NONCLINICAL TOXICOLOGY		13.2 Animal Toxicity and/or Pharmacology Daily administration of oral ibrexafungerp for 26 weeks in rats was associated with markedly severe phospholipidosis and foamy macrophages in alveolar cells in the lung which correlated with labored breathing, marked irritation and metaplasia in gastric mucosa, and peripheral nerve lesions accompanied by hind-limb paralysis. These effects occurred at plasma ibrexafungerp exposures approximately 10 times greater than plasma exposure associated with the RHD based on AUC comparison.
Reviewer's Comment: Information from long term animal toxicity studies has been added. Based on the labeling regulations, Subsection 13.2 is intended to describe significant animal data necessary for safe and effective use of the drug in humans that is not incorporated in other sections of labeling. The ibrexafungerp-related toxicities that occurred in the 26-week toxicity study in rats have not been reported in humans. However, awareness of these toxicities in rats may provide insights for physicians and patients should related adverse events emerge with longer durations of clinical ibrexafungerp administration. Refer to Section 5 for additional details.		
Section: 14 CLINICAL STUDIES	14.2 Prevention of RVVC "..... (b) (4) (intent to treat) was all randomized patients, consisting of 130 patients treated with BREXAFEMME and 130 patients treated with placebo. The average age was 34 years (range 18-65 years) with (b) (4) % less than 50 years. 90% were White and 8% were Black or African American, 8% were of Hispanic or Latino ethnicity. The average BMI was 25; 16.5% were obese (BMI >30). Efficacy was assessed as the percentage of patients with Clinical Success, defined as subjects with No Culture Proven, Presumed or Suspected Recurrence of VVC requiring antifungal therapy up to TOC at Week 24. (b) (4) The results for the clinical and	14.2 Reduction in the Incidence of RVVC "...The intent to treat (ITT) population was all randomized patients. The ITT population consisted of 130 patients treated with BREXAFEMME and 130 patients treated with placebo. The average age was 34 years (range 18-65 years) with 95% less than 50 years. About 90% patients were White and 8% were Black or African American. Eighth percent (8%) patients were of Hispanic or Latino ethnicity. The average BMI of the patient population was 25, and 16.5% were obese (BMI >30). Efficacy was assessed as the percentage of patients with Clinical Success, defined as subjects with No Culture Proven, Presumed or Suspected Recurrence of VVC requiring antifungal therapy up to TOC at Week 24. Clinical Success was also assessed at the Week 36 follow-up visit. Statistically significantly greater percentages of patients experienced Clinical Success at TOC with BREXAFEMME treatment compared to placebo. The clinical success rate at TOC was lower for patients in the United States when compared to patients outside the United States (ex-US) for both BREXAFEMME and placebo groups. In both regions, the BREXAFEMME group had a higher clinical success rate compared to placebo (US: 33% vs 23% and ex-US: 81% vs 68% in BREXAFEMME vs placebo

	(b) (4) are presented in Table 5.	arms respectively) and the difference between the treatment groups was consistent [US: 10.1% (-9.0, 29.1) and ex-US: 12.9% (0.04, 25.7)]. Clinical Success at Week 36 was also greater for BREXAFEMME compared to placebo. The results for the clinical success and reasons for clinical failure are presented in Table 5.																																																																																														
	Table 5. Clinical and Mycological Response, ITT Population <table><tr><th></th><th colspan="2">Trial 3</th></tr><tr><th></th><th>BREXAFEMME N = 130 n (%)</th><th>Placebo N = 130 n (%)</th></tr><tr><td>Clinical success at TOC (Week 24)</td><td>85 (65.4)</td><td>69 (53.1)</td></tr><tr><td>Difference (95% CI)</td><td colspan="2">12.7 (2.2, 23.1)</td></tr><tr><td>P-value</td><td colspan="2">0.020</td></tr><tr><td colspan="3"> (b) (4) </td></tr><tr><td>Clinical success at follow-up (Week 36)</td><td>75 (57.7)</td><td>60 (46.2)</td></tr><tr><td>Difference (95% CI)</td><td colspan="2">11.9 (1.1, 22.6)</td></tr><tr><td>P-value</td><td colspan="2">0.034</td></tr><tr><td colspan="3"> (b) (4) </td></tr></table> Abbreviations: CI = confidence interval; TOC = test of cure. (b) (4) Note: Subjects not meeting the definition of clinical success were considered clinical failure.		Trial 3			BREXAFEMME N = 130 n (%)	Placebo N = 130 n (%)	Clinical success at TOC (Week 24)	85 (65.4)	69 (53.1)	Difference (95% CI)	12.7 (2.2, 23.1)		P-value	0.020		(b) (4)			Clinical success at follow-up (Week 36)	75 (57.7)	60 (46.2)	Difference (95% CI)	11.9 (1.1, 22.6)		P-value	0.034		(b) (4)			Table 5. Clinical and Mycological Response, ITT Population <table><tr><th></th><th colspan="3">Trial 3</th></tr><tr><th></th><th>BREXAFEMME N = 130 n (%)</th><th>Placebo N = 130 n (%)</th><th>Difference (95% CI) P-value</th></tr><tr><td>Clinical success at TOC (Week 24)</td><td>85 (65.4)</td><td>69 (53.1)</td><td>12.7 (2.2, 23.1) 0.020</td></tr><tr><td>Reasons For Clinical Failure at TOC</td><td></td><td></td><td></td></tr><tr><td> Mycologically Proven</td><td>30 (23.1)</td><td>47 (36.2)</td><td></td></tr><tr><td> Recurrence</td><td>7 (5.4)</td><td>3 (2.3)</td><td></td></tr><tr><td> Presumed Recurrence</td><td>2 (1.5)</td><td>4 (3.1)</td><td></td></tr><tr><td> Suspected Recurrence</td><td>6 (4.6)</td><td>7 (5.4)</td><td></td></tr><tr><td> Imputed Recurrence</td><td></td><td></td><td></td></tr><tr><td>Clinical success at follow-up (Week 36)</td><td>75 (57.7)</td><td>60 (46.2)</td><td>11.9 (1.1, 22.6) 0.034</td></tr><tr><td>Reasons For Clinical Failure at follow-up</td><td></td><td></td><td></td></tr><tr><td> Mycologically Proven</td><td>37 (28.5)</td><td>51 (39.2)</td><td></td></tr><tr><td> Recurrence</td><td>8 (6.2)</td><td>5 (3.8)</td><td></td></tr><tr><td> Presumed Recurrence</td><td>4 (3.1)</td><td>5 (3.8)</td><td></td></tr><tr><td> Suspected Recurrence</td><td>6 (4.6)</td><td>9 (6.9)</td><td></td></tr><tr><td> Imputed Recurrence</td><td></td><td></td><td></td></tr></table> Abbreviations: CI = confidence interval; TOC = test of cure. Note: Subjects not meeting the definition of clinical success were considered clinical failure.		Trial 3				BREXAFEMME N = 130 n (%)	Placebo N = 130 n (%)	Difference (95% CI) P-value	Clinical success at TOC (Week 24)	85 (65.4)	69 (53.1)	12.7 (2.2, 23.1) 0.020	Reasons For Clinical Failure at TOC				Mycologically Proven	30 (23.1)	47 (36.2)		Recurrence	7 (5.4)	3 (2.3)		Presumed Recurrence	2 (1.5)	4 (3.1)		Suspected Recurrence	6 (4.6)	7 (5.4)		Imputed Recurrence				Clinical success at follow-up (Week 36)	75 (57.7)	60 (46.2)	11.9 (1.1, 22.6) 0.034	Reasons For Clinical Failure at follow-up				Mycologically Proven	37 (28.5)	51 (39.2)		Recurrence	8 (6.2)	5 (3.8)		Presumed Recurrence	4 (3.1)	5 (3.8)		Suspected Recurrence	6 (4.6)	9 (6.9)		Imputed Recurrence			
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Imputed Recurrence																																																																																																
Reviewer's Comment: A paragraph discussing the differences in success rates between US and Ex-US sites has been added. Additionally, Table 5 has been modified to include reasons for clinical failure. Additionally, the submitted PI did not include the updates made to the PI that was approved on 6/15/2022 for NDA 214900/S-001. Those updates were added to subsection 8.4 Pediatric Use; and subsection 8.6 Hepatic impairment as follows:																																																																																																
Section: 8 Subsection 8.4 Pediatric Use	The safety and effectiveness of BREXAFEMME for treatment of VVC have been established in post-menarchal pediatric females. Use of BREXAFEMME in postmenarchal pediatric patients is supported by evidence from adequate and well-controlled studies of BREXAFEMME in adult non-pregnant women with additional safety data from postmenarchal pediatric females [see Adverse Reactions (6.1), and Clinical Studies (14.1)].	The safety and effectiveness of BREXAFEMME for treatment of VVC have been established in post-menarchal pediatric females. Use of BREXAFEMME in post-menarchal pediatric patients is supported by evidence from adequate and well-controlled studies of BREXAFEMME in adult non-pregnant women with additional pharmacokinetic and safety data from postmenarchal pediatric females [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)].																																																																																														

Subsection 8.6 Hepatic Impairment		No dosage adjustment of BREXAFEMME is recommended in patients with mild hepatic impairment (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B). Administration of BREXAFEMME in patients with severe hepatic impairment (Child-Pugh Class C) has not been studied. <i>[see Clinical Pharmacology (12.3)]</i>.
Section: 12 CLINICAL PHARMACOLOGY Subsection 12.3 Pharmacokinetics		<u>Specific Populations</u> <i>Post-Menarchal Pediatric Females and Geriatric Patients</i> The pharmacokinetics of ibrexafungerp were not altered in postmenarchal pediatric females (ages 13 to 17 years) or in geriatric patients (ages 65 to 76 years). <i>Patients with Hepatic Impairment</i> The pharmacokinetics of ibrexafungerp were not altered in subjects with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment when the total AUC estimates were compared to healthy subjects. The impact of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of ibrexafungerp is unknown.

12.2 Patient Labeling

The Applicant submitted a Patient Package Insert (PPI) in this sNDA. Of note, the PPI was changed to a Medication Guide (MG) due to the addition of a Boxed Warning to the PI. For additional details, please refer to Section 12.1 above and the Patient Labeling Review in DARRTS (dated 11/4/2022).

13 Risk Evaluation and Mitigation Strategies (REMS)

The clinical review team and the Division of Risk Management (DRM) agree that a REMS is not necessary for the safe use of ibrexafungerp.

There were some additional risk management strategies that were agreed upon with the Applicant to mitigate the increased risk of inadvertent exposure to ibrexafungerp in pregnancy during the 6-month treatment period for the RVVC indication. In addition to the recommended labeling and ongoing post marketing study collecting prospective and retrospective data in women exposed to ibrexafungerp during pregnancy, a Medication Guide will be provided to

patients and a 'Dear Healthcare Provider Letter' will be used to communicate the need to verify pregnancy status in females of reproductive potential prior to starting ibrexafungerp treatment, advise patients to use effective contraception during treatment of VVC and throughout the 6-month treatment period for reduction in the incidence of RVVC, and the recommendation to reassess pregnancy status prior to each dose when ibrexafungerp is used monthly for 6 months for the reduction in the incidence of RVVC.

14 Postmarketing Requirements and Commitment

No additional PMRs or PMCs are proposed based on the review of this sNDA.

15 Division Director (Clinical) Comments

I agree with the review team's assessment and recommendations.

16 Appendices

16.1.

Financial Disclosure

Disclosure of financial interests of the investigators who conducted the clinical trials supporting this sNDA, including statements of due diligence in cases where the Applicant was unable to obtain a signed form from the investigator, was submitted in the FDA form 3454. These disclosures were certified by Glen D. Park, PharmD, MSJ, Vice President, Regulatory Affairs and Quality Assurance.

Covered Clinical Study (Name and/or Number): SCY-078-304

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>49</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time		

employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

RAMA KAPOOR
11/29/2022 06:50:15 PM

PETER W KIM
11/29/2022 06:53:46 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214900Orig1s002

OTHER REVIEW(S)

Pharmacovigilance Strategy (PVS)

Active Ingredient or Drug Class	ibrexafungerp
Drug Product(s)	NDA 214900 Brexafemme
Applicant(s), Manufacturer(s), or Compounder(s)	Scynexis, Inc
Product Approval Dates	June 1, 2021 -original application November 30, 2022- S-002
Task Tracking Tool #	2022-2284 (PVS maintenance)
PVS Lead	Neha Gada, PharmD Cross-Discipline Safety Advisor Office of Pharmacovigilance and Epidemiology
Date Completed	January 17, 2023
PVS Version	1.2

Template Version: November 2022

Pharmacovigilance Strategy Ibrexafungerp Drug Team Members by Discipline

The following staff contributed to development of the PVS monitoring plan and this document.

Office/Division	Name	Team Role
OSE/DEPI	Tracy Pham	Member
	Modupeola Adereti	Member
	Sheheryar Muhammad	Team Leader
	Natasha Pratt	Team Leader
	Jose Hernandez	Sentinel Core Team Member
	Monique Falconer	Deputy Director
OSE/DPV	Rajdeep Gill	Deputy Director
	Kate McCartan	Member
	Rachna Kapoor	Team Leader
	Sara Camilli	Associate Director
OND/DAI	Heidi Smith	NDA CDTL
	Rama Kapoor	Medical Officer
OND/DPMH	Jeannie Limpert	Medical Officer

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1 INTRODUCTION

The purpose of this pharmacovigilance strategy (PVS) is to modify the postmarket surveillance and risk management activities for ibrexafungerp, which include routine monitoring¹ and additional pharmacovigilance activities. This PVS is based upon data included in the NDA/BLA original and S-002 submissions and is updated with data available as of 30 November 2022. While this document includes information for the current PVS, it may be modified as safety information accumulates. CDER reviewers should refer to CDER's Lifecycle Signal Tracker (LiST) for the current PVS.

This PVS is designed to address CDER's monitoring plans for potential exposure to ibrexafungerp during pregnancy.

2 DRUG PRODUCT(S) OVERVIEW

2.1. DRUG PRODUCT AND APPLICATION

Ibrexafungerp NDA 214900

2.2. DRUG CLASS

Triterpenoid antifungal drug

2.3. APPROVED INDICATIONS

Treatment of adult and post-menarchal pediatric females for:

- Treatment of vulvovaginal candidiasis (VVC)
- Reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC)

2.1. MECHANISM OF ACTION

Triterpenoid antifungal drug, which inhibits glucan synthase, an enzyme involved in the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall. Ibrexafungerp has concentration-dependent fungicidal activity against *Candida* species as measured by time kill studies.

2.2. DOSING REGIMENS AND EXPECTED FREQUENCY/DURATION OF USE

- Treatment of vulvovaginal candidiasis (VVC): 150 mg tablet: two tablets twice a day x 1 day, with or without food, for total treatment dose of 600mg

¹ FDA, 2019, Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff

- Reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC) : 150 mg tablet: two tablets twice a day x 1 day per month, with or without food, for total treatment dose of 600mg monthly

2.3. OTHER RELEVANT INFORMATION

A Boxed Warning was added with the approval of the ibrexafungerp efficacy supplement 002 on November 30, 2022. The risk of inadvertent exposure during pregnancy is increased with intermittent and prolonged dosing regimen for the indication of RVVC. Thus, a boxed warning was added to mitigate the risk of a serious adverse reaction of fetal harm, that can be prevented by avoiding the use in pregnancy as a result of increased visibility to patient and providers with the addition of boxed warning.

WARNING: RISK OF EMBRYO-FETAL TOXICITY

- BREXAFEMME is contraindicated in pregnancy because it may cause fetal harm based on findings from animal reproductive studies. (4, 5.1)
- For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment. Reassessing pregnancy status prior to each dose is recommended when BREXAFEMME is used monthly for 6 months for reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC). (2.3, 5.1)
- Advise females of reproductive potential to use effective contraception during treatment of vulvovaginal candidiasis (VVC) and throughout the 6-month treatment period for reduction in the incidence of RVVC with BREXAFEMME and for 4 days after the last dose. (5.1, 8.3)]

3 DATA REVIEWED

The following data sources were reviewed to inform development of this PVS:

- Postmarket safety signals documented in LiST for ibrexafungerp
- Ibrexafungerp Supplement-002 common technical document (CTD) sections 2.5 Clinical Overview, and 2.7.4 Clinical Safety Summary; eCTD location(s):
<\\CDSESUB1\EVSPROD\nda214900\0036\m2\27-clin-sum\273-summary-clinical-efficacy.pdf>
- Ibrexafungerp approved labeling dated of November 30, 2022
- Ibrexafungerp Unireview.¹ November 29, 2022
- Ibrexafungerp Evaluation of Need for Risk Evaluation and Mitigation Strategy (REMS)² November 29, 2022

4 MONITORING PLANS FOR SAFETY CONCERNS

Monitoring plans for this PVS include routine and additional PV activities. Because routine PV is described elsewhere **Error! Bookmark not defined.** and is integrated into daily CDER processes,

additional description to detail the routine PV activities for the following data sources in this document is not necessary, unless determined otherwise by the PVS team.

- Relevant Investigational New Drug (IND) (i.e., same active ingredient and same sponsor, including across Divisions) 7-day safety reports: Routine monitoring of relevant IND safety reports
- FDA Adverse Event Reports (FAERS) and Published Medical Literature: DPV will conduct weekly monitoring of FAERS data and published medical literature. This monitoring applies risk-based principles and includes both broad and targeted monitoring for new safety concerns or new information about known safety concerns. When appropriate, the safety concerns listed in this PVS will be considered adverse events of interest during this routine monitoring.
- Postmarket Drug Safety Surveillance Summary: When appropriate, DPV will initiate a cumulative screening of data from multiple sources (e.g., FAERS, medical literature, periodic safety reports) to identify new safety concerns or new information about known safety concerns, including additional clinically important findings that inform the safety concerns identified in the PVS.
- Periodic Safety Reports (PSR): PSRs will be reviewed by OND for new information relevant to the identified safety concerns.

4.1. IMPORTANT POTENTIAL RISK

4.1.1. Potential Exposure During Pregnancy

Please refer to Ibrexafungerp NDA 214900 PVS Version 1.0³ dated September 29, 2021, for description of the risk identified in non-clinical studies. Notably, the risk characterization has changed with the RVVC indication. Specifically, the risk of inadvertent exposure during pregnancy is increased with intermittent and prolonged dosing regimen for the indication of RVVC.

4.1.2. Current Labeling

There has been no new safety information for ibrexafungerp since the time of approval of the original application in June 2021. However, with the introduction of the longer treatment duration of monthly for 6 months for the RVVC indication, the MAR team determined that highlighting this information in a new boxed warning, corresponding medication guide (previously patient information), and a Dear Health Care Provider Letter to increase visibility of this risk is essential.

- The prescribing information includes a new boxed warning for the risk of embryofetal toxicity, instructing prescribers to verify that the patient is not pregnant prior to initiating ibrexafungerp treatment, and to reassess pregnancy status prior to each dose when used monthly for 6 months for RVVC. It is also advised that females of reproductive potential use effective contraception during treatment of VVC and throughout the 6-month treatment period for RVVC and for 4 days after the last dose.
- The prescribing information includes a medication guide.

- The Applicant has stated that a Dear Health Care Provider Letter will be sent to potential prescribers of ibrexafungerp outlining the information in the boxed warning.

4.1.3. Monitoring Plans

The Applicant will continue to maintain their post-marketing pregnancy safety PMR in females exposed to ibrexafungerp to provide clinically relevant human safety data intended to inform healthcare providers caring for females of reproductive potential in the future.

We include two modifications to the PVS version 1.2 noted below.

1. Requested enhanced pharmacovigilance for cases of potential exposure to ibrexafungerp during pregnancy, including cases without an associated adverse event. The existing pregnancy PMR would The Applicant agreed with the Agency's request for enhanced pharmacovigilance (EPV). The conditions of the are reproduced from the ibrexafungerp S-002 approval Letter⁴ below:

We request that you perform postmarketing surveillance for exposure to ibrexafungerp during pregnancy. Submit all confirmed or possible cases of exposure to ibrexafungerp during pregnancy as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)) and include a narrative summary and analysis (as described under 21 CFR 314.80(c)(2)) of exposure during pregnancy as part of your required postmarketing safety reports [e.g., periodic safety reports].

2. During a PVS sub-team meeting held September 29, 2022, the PVS team, comprised of members from DPV, DEPI, Drug Use, DAI clinical, Sentinel Core Team, DPMH, discussed the ibrexafungerp PVS maintenance data, with focused discussion regarding recent findings from TriNetX data, an EHR data aggregator. TriNetX data showed that ibrexafungerp use in women was low, but there was a possibility that ibrexafungerp was used during pregnancy. After discussion, the PVS team concluded that due to caveats of interpreting TriNetX data, the low use of ibrexafungerp for VVC in women, and ibrexafungerp mitigation strategies currently in place, PVS team intends to reconvene when additional descriptive drug use data is available for discussion in early 2023. The PVS team agrees to conduct parallel analyses in TriNetX and Rapid Sentinel Distributive Database acknowledging strengths and limitations of each database and leveraging each database to bolster context to the discussion.

The PVS team agreed to meet sooner if other compelling data arise such as from case reports.

5 REFERENCES

1 Kapoor, Rama. NDA Multi-disciplinary review and evaluation 214900 S-002 November 29, 2022. DARRTS Ref ID 5085694

2 Boston, Naomi. NDA 214900 S-002 Evaluation of the Need for a REMS. November 29, 2022. DARRTS Ref ID 5085246

3 : Gada, N. NDA 214900 Ibrexafungerp Pharmacovigilance Strategy. Sept 20, 2021. DARRTS Ref ID 4859789

4 Kim, Peter. Ibrexafungerp NDA 214900 Supplement Approval Letter. November 30, 2022. DARRTS Ref ID 5086209

6 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES FOR IBREXAFUNGERP

Risk & Safety Concern (PMR # & NISS SSID, if applicable)	Monitoring Activity	Frequency and Duration of Monitoring	Discipline*	Comments/Notes
Important Potential Risk				
Exposure to ibrexafungerp during pregnancy Exposure to ibrexafungerp during pregnancy	Drug utilization monitoring	Every 6 months for the first 3 years post-approval, then annual thereafter. Completed checks in March, June, and September 2022. The next data check is January 2023. Updates regarding the timing of subsequent checks will be documented in CDER's LiST database.	Drug Use (lead) and Sentinel Core Team	- Office-based healthcare provider survey data - Manufacturer sales and dispensed prescription utilization data - TriNetX electronic healthcare record data - Sentinel administrative healthcare claim data
	Review of Periodic Safety Update	Quarterly for the first 3 years, then annual thereafter	OND Clinical	As part of enhanced pharmacovigilance, the Applicant agreed to include a narrative summary and analysis of ibrexafungerp exposure during

	Reports, including narrative summary and analysis of exposure during pregnancy			pregnancy as part of their required postmarketing safety reports [e.g., periodic safety reports]. OND clinical will share any concerning findings from these PSRs, with the PVS lead or during a PVS DT meeting. At this time, the PVS DT agrees a small number of cases of exposure during pregnancy would warrant information sharing across the DT. The PVS DT will reassess threshold of concern periodically based on drug uptake and other emerging data.
PMR 4069-1 single-arm descriptive pregnancy study	Single-arm pregnancy safety PMR to capture pregnancy outcomes	Interim Study Reports planned: 06/2023, 06/2024, 06/2025, 06/2026, 06/2027, 06/2028, 06/2029 Final Study Report: Submission: 12/2029	DPMH	Conduct a worldwide single-arm descriptive study that collects prospective and retrospective data in women exposed to BREXAFEMME (ibrexafungerp) during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life.
* Refer to Task Tracking Tool or PVS Project Manager for PVS team member PMR: Postmarketing Requirement DPMH: Division of Pediatric and Maternal Health OND: Office of New Drugs January 17, 2023 Version 1.2				

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/s/

NEHA GADA
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 28, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214900/S-002
Product Name and Strength:	Brexafemme (ibrexafungerp) Tablets, 150 mg
Applicant/Sponsor Name:	Scynexis, Inc. (Scynexis)
OSE RCM #:	2022-1125-5
TTT ID #:	2022-2644-3
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 25, 2022 for Brexafemme. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Brexafemme (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented our recommendations. Additionally, the Applicant confirmed via email on November 28, 2022 (Appendix B), that they intend to enclose the Medication Guide in each carton. Thus, we have no additional recommendations at this time.

^a Myers, D. Label and Labeling Review Memo for Brexafemme (NDA 214900/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 NOV 22. RCM No.: 2022-1125-4 and TTT ID # 2022-2644-2.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 25, 2022

Container label

(b) (4)



Carton labeling

(b) (4)

APPENDIX B. RESPONSE TO INFORMATION REQUEST RECEIVED VIA EMAIL ON NOVEMBER 28, 2022

From: Glen Park <glen.park@scynexis.com>
Sent: Monday, November 28, 2022 12:35 PM
To: Rodgers, Alison <Alison.Rodgers@fda.hhs.gov>
Subject: [EXTERNAL] RE: Carton and Container labeling - Question

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Hi Alison,

We are planning to include the medication guide inside the carton.

Glen D. Park, PharmD, MSJ
Vice President, Regulatory Affairs & Quality Assurance

SCYNEXIS

| Work: +1.201.884.5495 | Mobile: +1.212.945.8512
| glen.park@scynexis.com | www.scynexis.com |

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/s/

DEBORAH E MYERS
11/28/2022 02:16:55 PM

VALERIE S VAUGHAN
11/28/2022 02:38:09 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 22, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214900/S-002
Product Name and Strength:	Brexafemme (ibrexafungerp) Tablets, 150 mg
Applicant/Sponsor Name:	Scynexis, Inc. (Scynexis)
OSE RCM #:	2022-1125-4
TTT ID #:	2022-2644-2
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 21, 2022 for Brexafemme. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Brexafemme (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION AND RECOMMENDATIONS

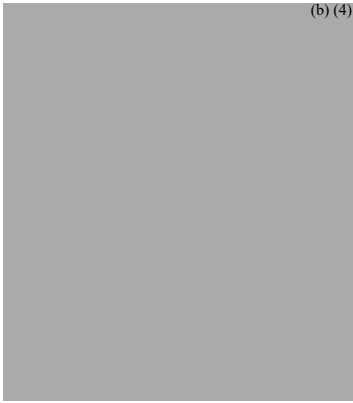
The container label and carton labeling can be improved from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our recommendations to minimize the risk for medication error in Section 3 for Scynexis, Inc.

3 RECOMMENDATIONS FOR SCYNEXIS, INC.

We recommend the following be implemented prior to approval of this sNDA:

^a Myers, D. Label and Labeling Review Memo for Brexafemme (NDA 214900/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 NOV 08. RCM No.: 2022-1125-3 and TTT ID # 2022-2644-1.

Table 1. Identified Issues and Recommendations for Scynexis, Inc. (Scynexis) (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	As currently presented, the statement “Avoid pregnancy (see accompanying information)” on the container label lacks prominence.	This important safety information, to alert patients that the product is contraindicated in pregnancy, could be overlooked if not prominently displayed on the container label.	To increase prominence of the statement “Avoid pregnancy (see accompanying information)” we recommend that you change the color of the font (e.g., red font) or highlight the statement. Additionally, we maintain our previous recommendation that the statement “Avoid pregnancy (see accompanying information)” be accompanied by a graphic symbol. The symbol is intended to serve as an additional aid to alert patients not to use this product if they are pregnant. For example:  Avoid Pregnancy (see accompanying information)
Carton Labeling			
1.	 (b) (4)	Warnings are considered to be “critical information” that should be prominently displayed on the principal display panel (PDP) of the container label and carton labeling. ^b	Relocate the Boxed Warning to the PDP. Additionally, we maintain our previous recommendation that you include a graphic symbol near the boxed warning. The symbol is intended to serve as an additional aid to alert patients not to use this product if they are pregnant.

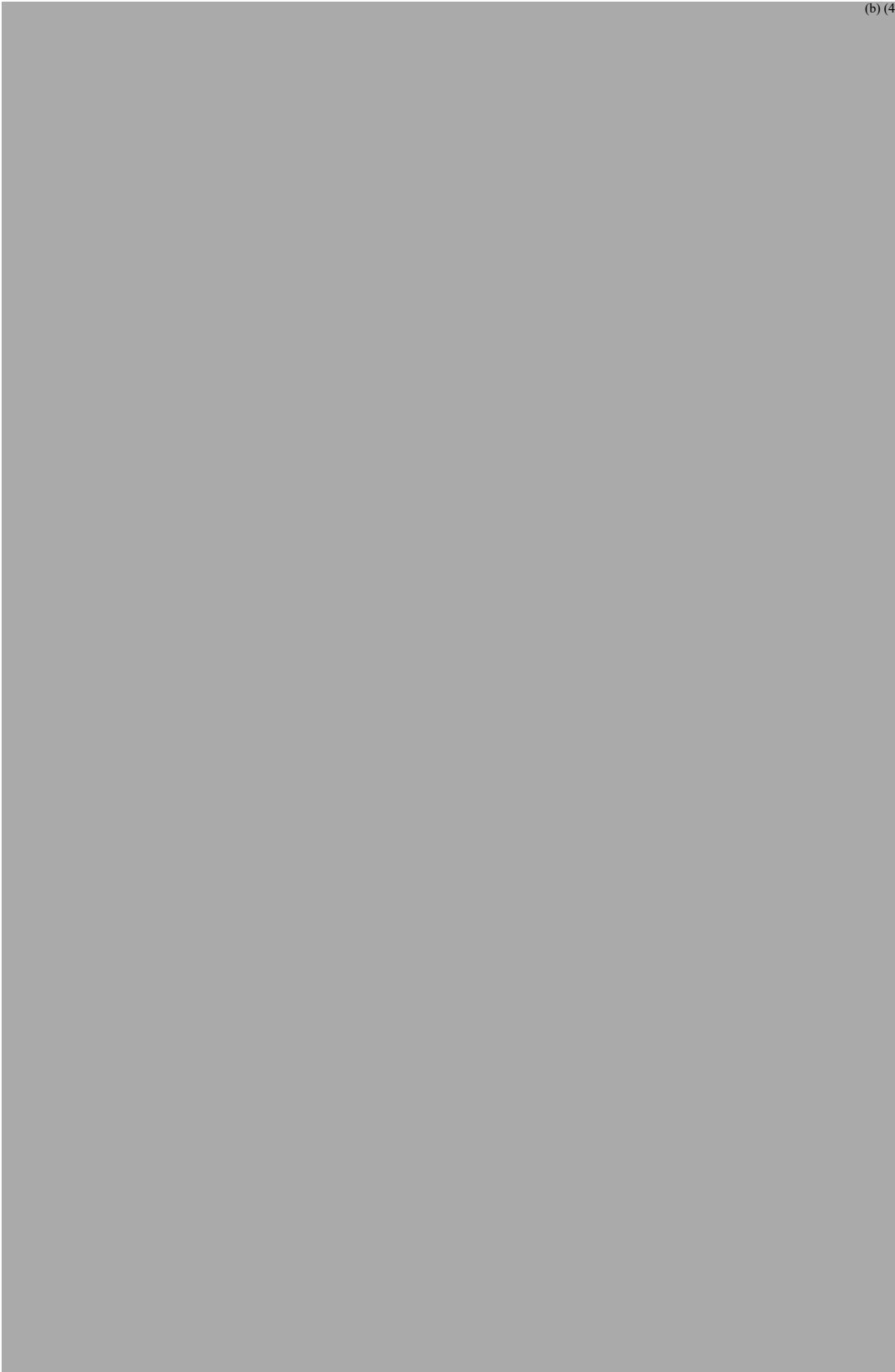
^b Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors>.

Table 1. Identified Issues and Recommendations for Scynexis, Inc. (Scynexis) (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			For example:  Contraindication/Warning: Avoid pregnancy. Do not take BREXAFEMME if you are pregnant or plan to become pregnant. Women who can become pregnant should use effective birth control throughout the duration of treatment with BREXAFEMME and for 4 days after the last dose of BREXAFEMME. (See accompanying information)

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 21, 2022

Container label



Carton labeling

(b) (4)

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/s/

DEBORAH E MYERS
11/22/2022 01:57:48 PM

VALERIE S VAUGHAN
11/22/2022 10:52:53 PM

Clinical Outcome Assessment Review Memorandum

From	Yasmin Choudhry, M.D. Clinical Outcome Assessment (COA) Reviewer Division of Clinical Outcome Assessment (DCOA) Selena Daniels, Pharm.D., Ph.D. COA Team Leader DCOA David Reasner, Ph.D. Division Director DCOA
To	Division of Anti-Infectives
COA tracking number	C2022237
sNDA# (Drug name)	214900 (Brexafemme® (ibrexafungerp tablets))
Drug Sponsor	SCYNEXIS Inc.
PDUFA Goal Date:	November 30, 2022
Indication:	• Treatment of vulvovaginal candidiasis (VVC) • Prevention of recurrent VVC (RVVC) ☒ Pediatric (b) (4)
Instrument(s) reviewed:	(b) (4)

In this submission, the applicant is seeking approval of Brexafemme® (ibrexafungerp tablets) for the prevention of recurrent vulvovaginitis candidiasis (RVVC). (b) (4)

(b) (4)

The primary objective of this review is to evaluate from a COA perspective if the submitted information supports the COA-related labeling claims related to this concept of interest.

(b) (4)

From a COA perspective, (b) (4) do not adequately support labeling claims as the instrument is not fit-for-purpose for the intended context of use.

Review Conclusions

Review Summary

The applicant did not submit an evidence dossier to support that the (b) (4) is fit-for-purpose for the context of this development program. As such, there is insufficient information to fully review (b) (4)

(b) (4)

Recommendations for Future Studies

(b) (4)

Regulatory Background and Materials Reviewed

BREXAFEMME® (ibrexafungerp tablets) for oral use was approved for the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis on June 1, 2021. Approval was based on data from Study SCY-078-304.

The materials reviewed for this submission included:

- 1.14.1.2 Annotated Draft Labeling Text – Efficacy Supplement (SDN 112; eCTD 0036)
- 2.7.3 Summary of Clinical Efficacy (SDN 112; eCTD 0036)
- 16.1.1 Protocol and Protocol Amendment Study SCY-078-304 (SDN 112; eCTD 0036)

Trial Design and Study Endpoints

Study SCY-078-304 is a multicenter, randomized, double-blind, placebo-controlled phase 3 study to evaluate the efficacy and safety of oral ibrexafungerp (formerly “SCY-078”) compared to placebo in female participants 12 years and older with RVVC.

The study consisted of a Screening visit, an Acute Phase with open-label fluconazole and a Prevention of Recurrence Phase with randomized ibrexafungerp or placebo. Screening and the beginning of the Acute Phase (Day -14) may occur on the same day. Approximately 320 subjects were planned to be enrolled into the open-label Acute Phase of the study in order to randomize approximately 240 subjects into the double-blind Prevention of Recurrence Phase, which consisted of 6 monthly, single-day treatments with randomized study drug.

Each subject was expected to complete the study within approximately 38 weeks.

A nested sub-study was made available to subjects who failed treatment with fluconazole during the Acute Phase and were not eligible for randomization into the Prevention of Recurrence Phase.

The study endpoints were:

Primary efficacy endpoint:

- Percentage of subjects with documented clinical success (defined as subjects having a test of cure [TOC] evaluation and no mycologically proven, presumed, or suspected recurrence of VVC) up to TOC (Week 24)

Secondary efficacy (b) (4) endpoints:

- Percentage of subjects with no mycologically proven recurrence (defined as an episode of VVC with a total composite score ≥ 3 on the VSS scale and a culture positive for *Candida* spp).

(b) (4)

Reviewer’s comment(s): *Per the Division, the subject of this review was restricted to the FSDS.*

For more details regarding the study design, refer to the Clinical review.

COA Description(s)

(b) (4)

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/s/

SELENA R DANIELS
11/09/2022 08:11:42 AM

DAVID S REASNER
11/09/2022 01:43:15 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 8, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214900/S-002
Product Name and Strength:	Brexafemme (ibrexafungerp) Tablets, 150 mg
Applicant/Sponsor Name:	Scynexis, Inc. (Scynexis)
OSE RCM #:	2022-1125-3
TTT ID #:	2022-2644-1
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

During our internal Wrap-Up Meeting held on November 18, 2022 for Brexafemme (NDA 214900/S-002), revisions to the Medication Guide (MG) text were proposed, discussed and agreed upon. Thus, the Division of Anti-Infectives (DAI) requested that DMEPA provide updates to their previous container label and carton labeling recommendations^a to reflect these revisions to the MG.

2 DISCUSSION, CONCLUSION, AND RECOMMENDATIONS

As previously written, the text in the MG was did not clearly specify the length of time that contraception needs to be used (i.e., for the entire 6 months of treatment for RVVC as opposed to the day of tablet administration plus 4 days afterwards of each month). Thus, the MG text was revised to clarify that use of effective birth control should occur "throughout the duration of treatment". Subsequently, our carton labeling language recommendations provided in our previous Label and Labeling Memo^a no longer align with the most recent revisions to the MG. Therefore, per DAI's request, we provide the identified medication error issues, our rationale

^a Myers, D. Label and Labeling Review Memo for Brexafemme (NDA 214900/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 NOV 07. RCM No.: 2022-1125-2 and TTT ID # 2022-2644.

for concern, and our revised proposed recommendations to minimize the risk for medication error in Section 3 for Scynexis, Inc.

3 RECOMMENDATIONS FOR SCYNEXIS, INC.

We recommend the following be implemented prior to approval of this sNDA:

Table 1. Identified Issues and Recommendations for Scynexis, Inc. (Scynexis) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	We note that a Boxed Warning is proposed for this product due to contraindication in pregnancy because it may cause fetal harm based on findings from animal reproductive studies. Additionally, females of reproductive potential should verify that they are not pregnant prior to initiating Brexafemme treatment and use effective contraception during treatment and for 4 days after the last dose.	This important safety information should be included on the container label to alert patient that the product is contraindicated in pregnancy.	To alert patients that this product is contraindicated in pregnancy, we recommend the container label include a warning statement accompanied by a graphic symbol to alert the patient not use this product if they are pregnant. For example:  Avoid pregnancy (see accompanying information)
Carton Labeling			
1.	We note that a Boxed Warning is proposed for this product due to contraindication in pregnancy because it may cause fetal harm based on findings from animal reproductive studies. Additionally, females of reproductive potential should verify that they are not	This important safety information should be included on the carton labeling to alert users that the product is contraindicated in pregnancy. Females of reproductive potential should verify that they are not pregnant prior to initiating Brexafemme treatment and use effective	To alert patients and healthcare providers that this product is contraindicated in pregnancy, we recommend you add a Warning statement to the carton labeling. Additionally, to increase the prominence we recommend that you box the text and use bold font, as noted, and red font for the title "Contraindication/Warning:".

Table 1. Identified Issues and Recommendations for Scynexis, Inc. (Scynexis) (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	pregnant prior to initiating Brexafemme treatment and use effective contraception throughout the duration of treatment with Brexafemme and for 4 days after the last dose of Brexafemme.	contraception during treatment and for 4 days after the last dose. Additionally, warnings are considered to be “critical information” that should be prominently displayed on the principal display panel (PDP) of the container label and carton labeling. ^b	Also, we recommend that you include a graphic symbol near the boxed warning to alert the patient not use this product if they are pregnant. For example:  Contraindication/Warning: Avoid pregnancy. Do not take BREXAFEMME if you are pregnant or plan to become pregnant. Women who can become pregnant should use effective birth control throughout the duration of treatment with BREXAFEMME and for 4 days after the last dose of BREXAFEMME. (See accompanying information)
2.	We note that the Brexafemme labeling will include a Medication Guide. However, as currently presented the proposed carton labeling does not include a statement instructing that the accompanying Medication Guide be dispensed to each patient.	21 CFR 208.24(d) requires <i>“The label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and</i>	Add the statement “Dispense the accompanying Medication Guide to each patient” or similar in a prominently displayed manner on the PDP.

^b Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors>.

Table 1. Identified Issues and Recommendations for Scynexis, Inc. (Scynexis) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		<i>shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner."</i>	

APPEARS THIS WAY ON ORIGINAL

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/s/

DEBORAH E MYERS
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VALERIE S VAUGHAN
11/08/2022 05:05:08 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 7, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214900/S-002
Product Name and Strength:	Brexafemme (ibrexafungerp) Tablets, 150 mg
Applicant/Sponsor Name:	Scynexis, Inc. (Scynexis)
OSE RCM #:	2022-1125-2
TTT ID #:	2022-2644
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 BACKGROUND AND PURPOSE OF MEMORANDUM

During an internal labeling meeting held on October 31, 2022 for Brexafemme (NDA 214900/S-002), the inclusion of a Boxed Warning in the proposed prescribing information (PI), as well as the development and inclusion of a Medication Guide, was discussed. Based on this information, DMEPA shared that the previously reviewed container label and carton labeling (Appendix A)^{a,b} will need to be revised to reflect the addition of the Boxed Warning and Medication Guide. Thus, the Division of Anti-Infectives (DAI) requested that DMEPA draft language to be included on the container label and carton labeling to be sent concurrently with labeling recommendations for the PI.

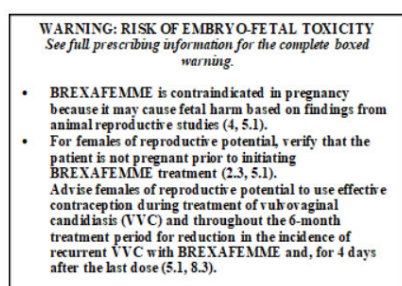
^a Myers, D. Label and Labeling Review for Brexafemme (NDA 214900/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 AUG 31. RCM No.: 2022-1125.

^b Myers, D. Label and Labeling Review for Brexafemme (NDA 214900/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 OCT 04. RCM No.: 2022-1125-1.

2 DISCUSSION, CONCLUSION, AND RECOMMENDATIONS

Brexafemme (ibrexafungerp) is approved for treatment of vulvovaginal candidiasis (VVC) with the recommended dose of two tablets twice a day for 1 day. The Applicant seeks to expand the indication to include prevention of recurrent VVC. The recommended duration of therapy for prevention of recurrent VVC would require therapy over 6 months. As such, DAI proposes that a Boxed Warning (see Figure 1) is added to the proposed PI for Brexafemme as the risk for embryofetal toxicity increases with prolonged ibrexafungerp use.

Figure 1. Proposed Boxed Warning for Brexafemme



Additionally, DAI proposes a Medication Guide is added. Considering DAI's proposed inclusion of a Boxed Warning in the PI, as well as the inclusion of a Medication Guide, the previously reviewed container label and carton labeling^{a,b} are no longer acceptable from a medication error perspective. The proposed container label and carton labeling may be improved to promote the safe use of this product from a medication error perspective. Thus, we provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 3 for Scynexis, Inc.

3 RECOMMENDATIONS FOR SCYNEXIS, INC.

We recommend the following be implemented prior to approval of this sNDA:

Table 1. Identified Issues and Recommendations for Scynexis, Inc. (Scynexis) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	We note that a Boxed Warning is proposed for this product due to contraindication in pregnancy because it may cause fetal harm	This important safety information should be included on the container label to alert patient that the product is	To alert patients that this product is contraindicated in pregnancy, we recommend the container label include a warning statement accompanied by a graphic

Table 1. Identified Issues and Recommendations for Scynexis, Inc. (Scynexis) (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	based on findings from animal reproductive studies. Additionally, females of reproductive potential should verify that they are not pregnant prior to initiating Brexafemme treatment and use effective contraception during treatment and for 4 days after the last dose.	contraindicated in pregnancy.	symbol to alert the patient not use this product if they are pregnant. For example: Avoid pregnancy  (see accompanying information)
Carton Labeling			
1.	We note that a Boxed Warning is proposed for this product due to contraindication in pregnancy because it may cause fetal harm based on findings from animal reproductive studies. Additionally, females of reproductive potential should verify that they are not pregnant prior to initiating Brexafemme treatment and use effective contraception during treatment and for 4 days after the last dose.	This important safety information should be included on the carton labeling to alert users that the product is contraindicated in pregnancy. Females of reproductive potential should verify that they are not pregnant prior to initiating Brexafemme treatment and use effective contraception during treatment and for 4 days after the last dose. Additionally, warnings are considered to be “critical information” that should be prominently displayed on the principal display panel	To alert patients and healthcare providers that this product is contraindicated in pregnancy, we recommend you add a Warning statement to the carton labeling. Additionally, to increase the prominence we recommend that you box the text and use bold font, as noted, and red font for the title “Contraindication/Warning:”. Also, we recommend that you include a graphic symbol near the boxed warning to alert the patient not use this product if they are pregnant. For example:

Table 1. Identified Issues and Recommendations for Scynexis, Inc. (Scynexis) (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		(PDP) of the container label and carton labeling. ^c	 Contraindication/Warning: Avoid pregnancy. Do not take BREXAFEMME if you are pregnant or plan to become pregnant. Women who can become pregnant should use effective birth control while taking BREXAFEMME and for 4 days after the last dose of BREXAFEMME. (See accompanying information)
2.	We note that the Brexafemme labeling will include a Medication Guide. However, as currently presented the proposed carton labeling does not include a statement instructing that the accompanying Medication Guide be dispensed to each patient.	21 CFR 208.24(d) requires <i>“The label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements</i>	Add the statement “Dispense the accompanying Medication Guide to each patient” or similar in a prominently displayed manner on the PDP.

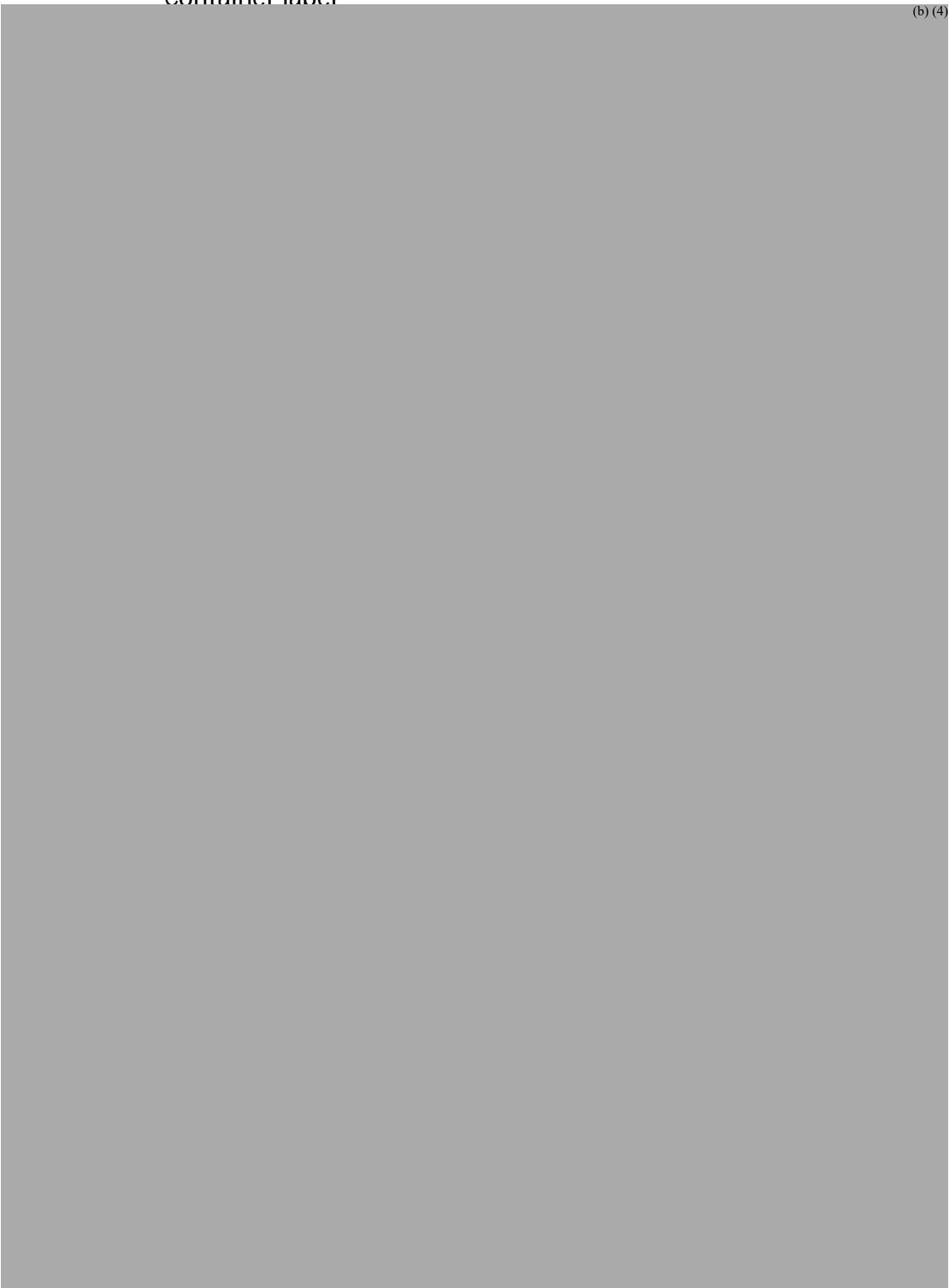
^c Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors>.

Table 1. Identified Issues and Recommendations for Scynexis, Inc. (Scynexis) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		<i>shall appear on the label in a prominent and conspicuous manner.”</i>	

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 29, 2022

Container label

(b) (4)



Carton labeling

(b) (4)



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/s/

DEBORAH E MYERS
11/07/2022 04:49:58 PM

VALERIE S VAUGHAN
11/07/2022 04:52:39 PM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 3, 2022

To: Alison Rodgers
Senior Regulatory Project Manager
Division of Anti-Infectives (DAI)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Mary Carroll, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Wendy Lubarsky, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Amended Review -Medication
Guide (MG)

Drug Name (established name): BREXAFEMME (ibrexafungerp)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 214900

Supplement Number: S-002

Applicant: Scynexis, Inc.

1 INTRODUCTION

On June 23, 2022, Scynexis, Inc. submitted for the Agency's review a Supplemental New Drug Application (NDA)-Efficacy Supplement for BREXAFEMME (ibrexafungerp) tablets, for oral use. The purpose of this submission is to support a new indication for the prevention of recurrent Vulvovaginal Candidiasis (VVC).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infectives (DAI) on August 4, 2022 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI), for BREXAFEMME (ibrexafungerp) tablets, for oral use. The DAI on November 2, 2022 requested that DMPP and OPDP review the applicant's amended PI for BREXAFEMME tablets, for oral use that now includes a black box warning and subsequently prompted a change from a PPI to a Medication Guide.

2 MATERIAL REVIEWED

- Draft BREXAFEMME (ibrexafungerp) PPI, received on June 23, 2022, and received by DMPP and OPDP on October 17, 2022.
- Draft BREXAFEMME (ibrexafungerp) Prescribing Information (PI) received on June 23, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 17, 2022.
- Draft BREXAFEMME (ibrexafungerp) Prescribing Information (PI) received on June 23, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 2, 2022

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

MARY E CARROLL
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11/04/2022 09:53:12 AM

MARCIA B WILLIAMS
11/04/2022 10:00:09 AM

LASHAWN M GRIFFITHS
11/04/2022 10:09:50 AM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: October 25, 2022

To: Alison Rodgers, Regulatory Project Manager
Division of Anti-Infectives (DAI)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for BREXAFEMME (ibrexafungerp tablets), for oral use

NDA: 214900/S-002

In response to DAI consult request dated August 3, 2022, OPDP has reviewed the proposed product labeling (PI) and the patient package insert (PPI) for BREXAFEMME (ibrexafungerp tablets), for oral use (Brexafemme). This supplement (S-002) is to support a new indication for the prevention of recurrent vulvovaginal candidiasis (RVVC).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAI (Alison Rodgers) on October 17, 2022, and we have no additional comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on October 25, 2022.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov.

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/s/

WENDY R LUBARSKY
10/25/2022 01:43:24 PM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: October 25, 2022

To: Alison Rodgers
Senior Regulatory Project Manager
Division of Anti-Infectives (DAI)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Mary Carroll, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Wendy Lubarsky, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): BREXAFEMME (ibrexafungerp)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 214900

Supplement Number: S-002

Applicant: Scynexis, Inc.

1 INTRODUCTION

On June 23, 2022, Scynexis, Inc. submitted for the Agency's review a Supplemental New Drug Application (NDA)-Efficacy Supplement for BREXAFEMME (ibrexafungerp) tablets, for oral use. The purpose of this submission is to support a new indication for the prevention of recurrent Vulvovaginal Candidiasis (VVC).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infectives (DAI) on August 4, 2022 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI), for BREXAFEMME (ibrexafungerp) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft BREXAFEMME (ibrexafungerp) PPI, received on June 23, 2022, and received by DMPP and OPDP on October 17, 2022.
- Draft BREXAFEMME (ibrexafungerp) Prescribing Information (PI) received on June 23, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 17, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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MARCIA B WILLIAMS
10/25/2022 09:42:03 AM

LASHAWN M GRIFFITHS
10/25/2022 09:47:52 AM

Clinical Inspection Summary

Date	October 17, 2022
From	Cheryl Grandinetti, PharmD Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Jacquelyn Rosenberger, Pharm.D., RPM Rama Kapoor, MD, Medical Reviewer Heidi Smith, MD, Medical Team Leader Peter Kim, MD, Division Director Division of Anti-Infectives (DAI)
NDA #	214900-S002
Applicant	Scynexis, Inc
Drug	Ibrexafungerp
NME	No
Proposed Indication	For the prevention of recurrent vulvovaginal candidiasis
Consultation Request	July 8, 2022
Summary Goal Date	October 26, 2022
Action Goal Date	November 30, 2022
PDUFA Date	November 30, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Chavoustie, Sorkin-Wells, and Delcheva-Zantina were inspected in support of NDA 214900-S002 (ibrexafungerp), covering one clinical trial, SCY-078-304. Overall, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

During the inspections, source records related to the primary efficacy endpoint data were verified against the sponsor's data line listings for all subjects randomized at these three sites (i.e., 48 subjects). No discrepancies were noted. These source records included the following:

- The investigator's and subject's vulvovaginal signs and symptoms (VSS) assessment performed at Screening, from Day -14 through Day -1, and then from Day 1 (Baseline) through Week 24, the Test of Cure (TOC) visit, and any unscheduled visit
- Concomitant use of additional antifungal therapy
- Mycological testing performed by the local laboratories at various timepoints during the trial (e.g., at screening visit and any time that a subject experienced a potential

recurrence), such as local testing of microscopic examination with 10% potassium hydroxide (KOH), vaginal pH measures, and wet mount examinations

- Central laboratory testing to rule out *Neisseria gonorrhoeae*, *Chlamydia trachomatis* or *Herpes virus* performed at the Screening visit and any time that a subject experienced a potential recurrence if any of these pathogens was suspected
- Central laboratory testing of fungal cultures and sensitivity testing performed at Screening, Baseline (Day 1), Week 12, Week 24 and any time that a subject experienced a potential recurrence

II. BACKGROUND

This NDA 214900-S002 was submitted in support of the use of oral ibrexafungerp for the treatment of subjects with recurrent vulvovaginal candidiasis (RVVC), a common fungal infection caused by *Candida* species. The pivotal study supporting the application was the following:

- **SCY-078-304**, “A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Ibrexafungerp (SCY 078) Compared to Placebo in Subjects with Recurrent Vulvovaginal Candidiasis.”

This was a phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of a 6-month dosing regimen of oral ibrexafungerp to prevent recurrences in adult subjects with RVVC. The primary objective was to evaluate the efficacy of oral ibrexafungerp versus placebo in preventing recurrences of VVC in subjects with RVVC based on clinical success.

- **Subjects:** A total of 530 subjects were screened; 440 subjects entered the Acute Phase; 260 subjects entered the Prevention of Recurrence Phase (i.e., 130 subjects each randomly assigned to ibrexafungerp group and placebo group)
- **Sites:** 49 study sites in the Poland (5 sites), Bulgaria (12 sites), Russia (6 sites), and USA (26 sites)
- **Study initiation and completion dates:** Oct 21, 2019 (first subject, first visit) to Nov 29, 2021 (last subject, last visit)
- **Database Lock Date:** Jan 25, 2022
- **Study Unblinding Date:** Jan 25, 2022

The study consisted of the following:

- A Screening Visit (Days -16 to -14)
- An Open-Label Acute Phase (with open-label fluconazole) (Days -14 to -1)
- A Prevention of Recurrence Phase (with randomization to ibrexafungerp or placebo) which included the following:

- Study Treatment Period (from Baseline, Day 1 to Test of Cure Visit, Week 24)
- Follow-Up Period (from Week 25 to Week 36, the End-of-Follow-Up Visit (EOFU))

Subjects eligible for inclusion had to have a diagnosis of symptomatic VVC that met the following criteria at Screening:

- A total composite score of ≥ 4 on the vulvovaginal signs and symptoms (VSS) scale
- Positive microscopic examination with 10% potassium hydroxide (KOH) in a vaginal sample collected at Screening revealing yeast forms (hyphae/pseudohyphae) or budding yeasts
- Normal vaginal pH (≤ 4.5)
- A minimum of 3 episodes of VVC in the past 12 months, including the current episode, that required administration of antifungal medication. Besides the current episode, at least 1 of the previous episodes in the past 12 months was required to have been a physician-diagnosed episode of VVC, with at least 1 positive test confirming vaginal yeast infection (e.g., KOH, culture, or fungal polymerase chain reaction).

Subjects who met all study eligibility criteria entered the Open-Label Acute Phase of the study and received treatment with open-label oral fluconazole 150 mg once a day on Days -14, -11, and -8. Study visits were scheduled on Day -14 (which could have been combined with the Screening visit), Day -11 and Day -8 (phone contacts). Subjects were dispensed fluconazole supplies and subject diaries (paper format) where they rated their vulvovaginal symptoms and recorded dosing details, adverse events (AEs), and concomitant medication use. Subjects took their first dose of fluconazole on Day -14 at the study site after all other visit procedures were done. Subjects self-administered the remaining doses at home.

The double-blind **Prevention of Recurrence Phase** consisted of 6 monthly, single-day treatments with randomized study drug. Subjects who had a culture-confirmed VVC from the sample collected at Screening, achieved a significant resolution of the signs and symptoms of infection (total composite score ≤ 2 on the VSS scale) at Baseline (Day 1) of this phase and continued to meet all study eligibility criteria were stratified (based on the presence or absence of uncontrolled diabetes, defined as hemoglobin A1c levels $\geq 8.00\%$ at Baseline and by geographical region of USA or Ex-USA) and randomized in a 1:1 ratio via an Interactive Web Response System (IWRS) to one of the following treatment groups:

- Oral ibrexafungerp, administered as a single-day treatment repeated every 4 weeks (28 days [± 3]) for a total of 6 single-day treatments (Baseline [Day 1], Week 4, Week 8, Week 12, Week 16, and Week 20). Each single-day treatment consisted of 2 doses of 300 mg each given 12 (± 4) hours apart (total single-day dose = 600 mg).
- Matching oral placebo

Subjects received their first dose of double-blind study drug at the site and self-administered the remaining doses at home. Study visits consisted of scheduled on-site visits, phone contacts, and lab visits (Acute Phase only) as well as unscheduled visits. Phone contacts were conducted to check for AEs, treatment compliance, potential recurrence, and concomitant medication use, including other antifungal agents. Unscheduled visits were conducted anytime that there were symptoms indicating a potential recurrence or an AE.

During the FU Period, an on-site study visit was scheduled at Week 36 (EOFU) and phone contacts were conducted at Weeks 28 and 32 to check for potential recurrence and antifungal medication use.

Fungal cultures were performed centrally at Screening, Baseline (Day 1), Week 12, Week 24 (TOC), Week 36 (EOFU) and any time that a subject experienced a potential recurrence (including both scheduled and unscheduled visits) for species identification and susceptibility testing. Positive cultures were also tested for susceptibility against ibrexafungerp, fluconazole and additional antifungal agents, as deemed appropriate based on validated methods.

The **primary efficacy endpoint** was the percentage of subjects with documented clinical success (defined as subjects having a TOC evaluation and no mycologically proven, presumed, or suspected recurrence of VVC up to TOC [Week 24]). Subjects were assessed for potential recurrence at all visits during the Study Treatment Period following Baseline (Day 1), including phone contacts, scheduled visits, and unscheduled visits.

The Intent-to-Treat (ITT) analyses were considered primary, and the Modified Intent-to-Treat (mITT) and Per-Protocol (PP) analyses were considered supportive of the primary analyses on the ITT population. The ITT Set included all randomized subjects who received at least one dose of study drug (ibrexafungerp or placebo).

The protocol defined the following three categories of recurrences of VVC:

- **Mycologically Proven Recurrence:** An episode of VVC with a total composite score ≥ 3 on the VSS Scale and a culture positive for *Candida* spp. that required antifungal treatment.
- **Presumed Recurrence:** An episode of VVC with a total composite score ≥ 3 on the VSS Scale that required antifungal treatment and for which there is a positive KOH microscopy but no positive fungal culture.
- **Suspected Recurrence:** An episode of VVC that required treatment with an antifungal agent (including self-administration with over-the-counter antifungals) regardless of VSS composite score or whether there is no mycological evidence of disease.

Investigator recorded signs of infection (i.e., edema, erythema and excoriation or fissures) on a VSS Scale template worksheet provided by the sponsor. The study coordinator or data entry designee at the site then transcribed the data from the source document (study worksheet) into the corresponding eCRF page.

Subjects recorded their symptoms of infection (i.e., itching, burning and irritation) in the paper diary provided by the sponsor on a weekly basis and at the time of each scheduled or unscheduled visit and brought the diary to each visit. The study coordinator collected the diary at each visit and transcribed the data from the diary into the corresponding eCRF page. If the diary was not returned by the subject or the entry for the date of the visit was missing, the study coordinator was instructed to ask the subject for their symptoms for the visit date and record them in the subject's source document, with subsequent transcription into the eCRF page.

The following test results and information were used to assess mycological outcomes:

- Direct wet mount microscopic examination to visualize clue cells indicative of bacterial vaginosis or trichomonas performed at the site or a local laboratory
- Direct microscopic examination with 10% KOH to identify yeast performed at the site or a local laboratory
- A vaginal sample processed by a central laboratory (i.e., (b) (4)) to rule out vulvovaginitis and/or cervicitis caused by Herpes virus, Neisseria gonorrhoeae, or Chlamydia trachomatis infection
- Fungal cultures and susceptibility testing performed by the central laboratories (i.e., (b) (4))
- Documentation of additional antifungal treatment used by the subjects

The direct wet mount and KOH microscopic examinations were performed locally at Screening for the determination of subject eligibility and then anytime that a recurrence was suspected.

If the investigator suspected herpes virus, Neisseria gonorrhoeae or Chlamydia trachomatis infection, a vaginal sample was collected and sent to (b) (4), the designated central laboratory to conduct such testing.

The designated central laboratories used to perform fungal culture and susceptibility testing were as follows:

(b) (4)

Rationale for Site Selection

In general, the clinical sites were chosen primarily based on numbers of enrolled subjects, site-specific efficacy pertinent to decision-making, and inspectional history. In addition, Site 160 had high site-specific efficacy (i.e., 7 of the 8 subjects randomized to ibrexafungerp were deemed responders) and was a driver of efficacy.

II. RESULTS (by site):

1. Steven Chavoustie, MD

Site #160

1065 Northeast 125th Street

Suite 102

North Miami, FL 33161

Inspection Dates: August 29 to 31, 2022

At this site, 47 subjects were screened, 17 subjects entered the Prevention of Recurrence Phase and were randomized, and 13 subjects completed the study. Four subjects terminated early: three were lost to follow-up (Subject (b) (6), (b) (6) and (b) (6) all randomized to placebo) and one subject terminated early due to an adverse event (Subject (b) (6) randomized to placebo; adverse event of thrombocytopenia).

An audit of the study records for the 17 randomized subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records, laboratory reports, and other regulatory documentation (e.g., Form FDA 1572s, financial disclosures); primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records for the primary efficacy endpoint variables related to clinical success (i.e., the investigator's and subject's VSS assessment completed at the Baseline Visit through the Week 24 TOC Visit; concomitant use of additional antifungal therapy; testing to rule out *Neisseria gonorrhoeae*, *Chlamydia trachomatis* or herpes virus; and mycological testing performed by the local and central laboratories) were reviewed and verified against the sponsor's data line listings for all 17 subjects who were randomized. No discrepancies were noted.

2. Valerie Sorkin-Wells, MD

Site #156

3805 E. Bell Road

Phoenix, AZ 85032

Inspection Dates: August 22 to 26, 2022

At this site, 44 subjects were screened, 14 subjects entered the Prevention of Recurrence Phase and were randomized, and 12 subjects completed the study. Two subjects terminated early. One subject withdrew consent because the subject's schedule no longer allowed for study participation (Subject (b) (6) randomized to ibrexafungerp), and the second subject was lost to follow-up (Subject (b) (6) randomized to placebo).

An audit of the study records for the 44 screened subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records, laboratory reports, and other regulatory documentation (e.g., Form FDA 1572s, financial disclosures); primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records for the primary efficacy endpoint variables related to clinical success (i.e., the investigator's and subject's VSS assessment completed at the Baseline Visit through the Week 24 TOC Visit; concomitant use of additional antifungal therapy; testing to rule out *Neisseria gonorrhoeae*, *Chlamydia trachomatis* or herpes virus; and mycological testing performed by the local and central laboratories) were reviewed and verified against the sponsor's data line listings for all 14 subjects who were randomized. No discrepancies were noted.

3. Dimka Delcheva-Zantina, MD

Site #458

1 Svoboda Square

Dupnitsa, 2600

Bulgaria

Inspection Dates: October 10 to 14, 2022

At this site, 21 subjects were screened, 17 subjects entered the Prevention of Recurrence Phase and were randomized, and all 17 subjects completed the study.

An audit of the study records for the 17 randomized subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Ethics Committee submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records, laboratory reports, and other regulatory documentation (e.g., Form FDA 1572s, financial disclosures); primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was one unreported adverse event of recurrence of diarrhea in Subject (b) (6) (randomized to ibrexafungerp on (b) (6)) that occurred on (b) (6), resolved on (b) (6), and was characterized by the investigator as not serious and mild, and deemed related to the study drug. This subject had a previously reported incident of diarrhea on (b) (6), that occurred during the Open-Label Acute Phase of the trial, which was also noted to have resolved on its own.

Reviewer's comment: *The unreported adverse event of diarrhea that occurred on (b) (6) in Subject (b) (6) is unlikely to impact the overall safety results of the study. This issue was discussed with Dr. Delcheva-Zantina during the inspection close-out meeting. Dr. Delcheva-Zantina acknowledged the under-reporting and promised improvements in the future.*

The source records for the primary efficacy endpoint variables related to clinical success (i.e., the investigator's and subject's VSS assessment completed at the Baseline Visit through the Week 24 TOC Visit; concomitant use of additional antifungal therapy; testing to rule out *Neisseria gonorrhoeae*, *Chlamydia trachomatis* or herpes virus; and mycological testing performed by the local and central laboratories) were reviewed and verified against the sponsor's data line listings for all 17 subjects who were randomized. No discrepancies were noted.

{See appended electronic signature page}

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

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Division of Pediatrics and Maternal Health Review

Date: October 7, 2022 **Date consulted:** June 16, 2022

From: Jean Limpert, MD, Medical Officer, Maternal Health Team (MHT)
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, MHT, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Anti-Infectives (DAI)

Drug: Brexafemme (Ibrexafungerp) tablet

NDA: 214900

Applicant: Scynexis Inc.

Subject: Labeling Updates for Females of Reproductive Potential

Approved

Indication: For the treatment of adult and post-menarchal pediatric females with
vulvovaginal candidiasis (VVC)

Proposed

Indication: For the prevention of recurrent vulvovaginal candidiasis (RVVC)

Materials

Reviewed:

- DPMH consult request dated June 16, 2022, DARRTS Reference ID 5000173
- Applicant's submitted background package and proposed labeling for NDA 214900

- DPMH labeling review for BREXAFEMME (Ibexafungerp), NDA 214900, March 29, 2021, Niquiche Guity, PhD, Clinical Analyst, DARRTS Reference ID 4769878
- DPMH labeling review for Oteseconazole, NDA 215888, November 10, 2021, Wenjie Sun, MD, Medical Officer, DARRTS Reference ID 4886476¹

Consult Question: “Currently, the drug product is contraindicated during pregnancy because of animal studies showing possible risks of fetal malformations with drug exposure. However, with the proposed indication, treatment is given over a lengthier period, thus making contraception/protection from drug exposure more complicated and likely requiring changes in the current labeling language.”

INTRODUCTION AND BACKGROUND

On May 31, 2022, Scynexis submitted an efficacy supplement for BREXAFEMME (ibexafungerp) for the proposed indication of prevention of RVVC. On June 16, 2022, DAI consulted DPMH to assist with updates to the language for females of reproductive potential.

Regulatory History

- Brexafemme (ibexafungerp) is a first-in-class antifungal agent. Brexafemme was initially approved on June 1, 2021 as a one-day regimen for the treatment of VVC in adults and post-menarchal female patients. In this submission, the applicant proposes a single-day dosing regimen each month for six months for the prevention of RVVC.
- Ibexafungerp is also in development as (b) (4) oral and intravenous glucan synthesis inhibitor for the treatment (b) (4) of fungal infections caused by *Candida* and *Aspergillus* species.²

Reviewer comment: The review team is currently planning to modify the proposed indication to reduction in the incidence of RVVC in post-menarchal females.

Drug Characteristics³

- *Drug class:* triterpenoid antifungal
- *Mechanism of Action:* inhibits glucan synthase, an enzyme involved in the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall.
- *Molecular weight:* 922 grams per mole
- *Half-life:* 20 hours
- *Protein binding:* >99%
- *Bioavailability:* 26%
- *Approved dosing regimen for VVC treatment:* 300 mg administered 12 hours apart for one day (total daily dosage 600 mg)
- *Proposed dosing regimen for prevention of RVVC:* 300 mg administered 12 hours apart for one day (total daily dosage 600 mg) monthly for six months

¹ The Oteseconazole review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

² Summary of Clinical Safety for Brexafemme, NDA 214900, page 5.

³ BREXAFEMME labeling, last revised June 15, 2022

Reviewer comment: DPMH discussed with the Clinical Pharmacology team whether accumulation with multiple doses of ibrexafungerp could occur such that there is a need to modify the currently stated interval to remain on contraception four days after the final dose of treatment based on the half-life. While there does appear to be some accumulation, it does not clearly influence the half-life and there is not a pharmacokinetic reason to justify a longer washout period.

Current State of the Labeling for Brexafemme⁴

- Current labeling is in PLLR format
- No Boxed Warning
- Contraindication for Pregnancy
- Warning and Precaution for Risk of Fetal Toxicity based on findings from animal studies. In embryo-fetal development studies, oral ibrexafungerp administration to pregnant rabbits at clinically relevant exposures (5 times the human exposure at the recommended human dose) was associated with rare malformations in rabbits.
- Verify the pregnancy status in females of reproductive potential prior to initiating treatment.
- Use of effective contraception during treatment and for four days after the last dose
- No known drug-drug interactions with hormonal contraceptives

REVIEW

RVVC⁵

- RVVC is a disorder characterized by three or more symptomatic episodes of VVC within 12 months. Most females with RVVC have no apparent predisposing or underlying conditions but it can occur secondarily from frequent antibiotic use or diabetes.⁶ The incidence and prevalence of RVVC is difficult to estimate due to self-diagnosis and self-treatment with over the counter medications.^{7,8} An online survey of more than 6,000 females estimated the lifetime prevalence of RVVC as approximately 9%, with the highest prevalence in females 25 to 34 years old (12%).^{9,10}
- Episodes of VVC are most commonly caused by *Candida albicans* but can be caused by other *Candida* species or yeasts. Recurrent disease is usually due to relapse from a persistent vaginal reservoir of the fungal pathogen that emerges to cause relapse or by reinfection with identical strain. In rare cases, a new strain of *Candida* is responsible

⁴ BREXAFEMME labeling, last revised June 15, 2022

⁵ Unireview for BREXAFEMME, NDA 214900, June 1, 2021, page 19.

⁶ Workowski KA, Bachmann LH, Chan PA, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep 2021;70(No. RR-4):1–187.

⁷ Blostein F, Levin-Sparenberg E, Wagner J, Foxman B. Recurrent vulvovaginal candidiasis. Ann Epidemiol. 2017 Sep;27(9):575-582.e3. doi: 10.1016/j.annepidem.2017.08.010. Epub 2017 Aug 15. PMID: 28927765.

⁸ Sobel, JD. Candida vulvovaginitis: Treatment. UpToDate. Accessed 9/7/22.

⁹ Collins, Laura M. MD1; Moore, Rachelle MD2; Sobel, Jack D. MD2. Prognosis and Long-Term Outcome of Women With Idiopathic Recurrent Vulvovaginal Candidiasis Caused by *Candida albicans*. Journal of Lower Genital Tract Disease: January 2020 - Volume 24 - Issue 1 - p 48-52

¹⁰ Nyirjesy, Paul et al. “Vulvovaginal Candidiasis: A Review of the Evidence for the 2021 Centers for Disease Control and Prevention of Sexually Transmitted Infections Treatment Guidelines.” Clinical infectious diseases. 74.Supplement_2 (2022): S162–S168. Web.

for the infection.^{11,12} *Candida glabrata* and other non-*albicans* *Candida* species are observed in 10%–20% of women with RVVC.¹³

- RVVC treatment (non-pregnant population): The recommended treatment for an episode of VVC is a short course of oral or intravaginal azole therapy. For RVVC, the recommended treatment is an intravaginal azole for 7-14 days or 3 doses of oral fluconazole followed by a suppressive maintenance regimen of oral fluconazole 150 mg once weekly for six months. Suppressive therapy, however, is rarely curative and recurrence is common after discontinuation of therapy.^{14,15}
- RVVC treatment (pregnant population): During pregnancy, treatment is primarily for relief of symptoms as vaginal candidiasis is not associated with adverse pregnancy outcomes. The recommended treatment for both VVC and RVVC are use of intravaginal azoles because of the potential risks of oral azole therapy during pregnancy, which include possible risk of miscarriage and an unclear association with birth defects.¹⁶
- In April 2022, Oteseconazole, a new oral azole antifungal, was approved to reduce the incidence of RVVC in females with a history of RVVC who are not of reproductive potential. Oteseconazole is contraindicated in females of reproductive potential and during pregnancy due to the potential for embryo-fetal toxicity based on animal studies and the preclusion of contraception recommendations for inclusion in labeling use due to the drug's long half-life and persistence in body tissues.

Clinical Experience

The applicant conducted a Phase 3, randomized, double-blind, placebo-controlled trial¹⁷ to evaluate the efficacy and safety of oral ibrexafungerp compared to placebo in post-menarchal women 12 years and older with a history of RVVC (n=260). Patients in the ibrexafungerp arm (n=130) were treated with their proposed dosing for RVVC (i.e., 300 mg twice a day, as a single day treatment repeated monthly for a total of six single-day treatments). Pregnant patients were excluded. Four subjects became pregnant during the study, one of whom was treated with ibrexafungerp. For the other three pregnancies, two subjects were in the placebo arm, and one subject became pregnant prior to randomization of treatment. Additional details for the pregnancy following ibrexafungerp exposure is described below.

¹¹ https://www.uptodate.com/contents/candida-vulvovaginitis-treatment?sectionName=RECURRENT%20VULVOVAGINAL%20CANDIDIASIS&search=recurrent%20vulvovaginal%20candidiasis&topicRef=5452&anchor=H154650914&source=see_link#H154650914

¹² Collins, Laura M. MD1; Moore, Rachele MD2; Sobel, Jack D. MD2. Prognosis and Long-Term Outcome of Women With Idiopathic Recurrent Vulvovaginal Candidiasis Caused by *Candida albicans*. *Journal of Lower Genital Tract Disease*: January 2020 - Volume 24 - Issue 1 - p 48-52

¹³ Workowski KA, Bachmann LH, Chan PA, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. *MMWR Recomm Rep* 2021;70(No. RR-4):1–187.

¹⁴ Nyirjesy, Paul et al. “Vulvovaginal Candidiasis: A Review of the Evidence for the 2021 Centers for Disease Control and Prevention of Sexually Transmitted Infections Treatment Guidelines.” *Clinical infectious diseases*. 74.Supplement 2 (2022): S162–S168. Web.

¹⁵ Workowski KA, Bachmann LH, Chan PA, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. *MMWR Recomm Rep* 2021;70(No. RR-4):1–187.

¹⁶ Sobel, JD. *Candida vulvovaginitis: Treatment*. UpToDate. Accessed 9/8/22.

¹⁷ Study name: CANDLE 304; SCY-078

Subject # (b) (6) 37-year-old female with acute VVC became pregnant during the study. She received three 150 mg doses of Fluconazole followed by two 300 mg doses of ibrexafungerp at baseline, week 4 and week 8 of the study (last dose of ibrexafungerp given on day 59). Concomitant medications also included levonorgestrel. The subject reported pregnancy on day 79 and was subsequently withdrawn from the study. The subject had a normal pregnancy and delivered a healthy newborn.¹⁸

The applicant did not report any postmarketing cases of pregnancy.

Review of Literature

Applicant's Review of Literature

The applicant did not identify relevant literature.

DPMH Review of Literature

DPMH performed a search in PubMed, Embase, Micromedex,¹⁹ TERIS,²⁰ REPROTOX,²¹ and *Drugs in Pregnancy and Lactation*²² to find relevant articles related to the use of ibrexafungerp during pregnancy. Search terms included “ibrexafungerp” AND “pregnancy,” “pregnant women,” “birth defects,” “congenital malformations,” “stillbirth,” “spontaneous abortion,” “miscarriage,” “fetal loss,” “fertility,” “infertility,” “contraception,” and “oral contraceptives.” Micromedex and TERIS do not cite literature for ibrexafungerp. Ibrexafungerp is not referenced in REPROTOX or *Drugs in Pregnancy and Lactation*. Relevant publications were not identified in Embase or PubMed.

DISCUSSION AND CONCLUSIONS

Approved labeling for Brexafemme includes a Warning and Precaution for the risk of fetal toxicity, a Contraindication for use during pregnancy, and recommendations for assessing pregnancy status prior to initiating treatment and use of effective contraception during treatment and for four days after completion of treatment. The proposed indication, to prevent RVVC, entails monthly administration of ibrexafungerp for six months. To minimize the risk of ibrexafungerp exposure during pregnancy, DPMH recommends updating Subsection 8.3 Females and Males of Reproductive Potential with a statement specifically for the RVVC indication to recommend that females of reproductive potential remain on contraception throughout the entire six month treatment and for four days after the last dose. Regarding assessment of pregnancy, approved labeling states “verify pregnancy status” prior to initiating treatment. For additional clarity, DPMH instead recommends “verify that the patient is not pregnant” prior to initiating treatment so that it is clear that ibrexafungerp should not be used during pregnancy. The assessment of pregnancy status throughout treatment was considered, particularly because the proposed indication is for the reduction in incidence of RVVC, a non-life-threatening condition. DPMH discussed with DAI and agreed that recommendation for initial verification of pregnancy status and the additional statement about contraception use throughout the six month treatment is likely adequate to mitigate the risk of unintentional ibrexafungerp exposure during pregnancy.

¹⁸ Applicant's submission for NDA 214900, SCY-078-304 Study Report, pages 194-198.

¹⁹ <https://www.micromedexsolutions.com>, accessed 9/1/22

²⁰ Truven Health Analytics information. TERIS, accessed 9/1/22

²¹ Truven Health Analytics information. REPROTOX, accessed 9/1/22

²² Briggs GG, Freeman RK. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. 12th edition. 2022, Philadelphia, PA. online, accessed 9/1/22

LABELING RECOMMENDATIONS

DPMH revised subsections 2.3, 5.1, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on 9/21/22. DPMH recommendations are below and reflect the discussions with DAI. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----DOSAGE AND ADMINISTRATION -----

- For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment (2.3)

-----CONTRAINDICATION-----

- Pregnancy (8.1)

-----WARNING AND PRECAUTIONS -----

- Risk of Fetal Toxicity: May cause fetal harm based on animal studies. Advise females of reproductive potential to use effective contraception during treatment and for 4 days after the last dose. (2.3, 5.1, 8.1, 8.3)

FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION

2.3 Pregnancy Evaluation Prior to Initiating Treatment

For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment with Brexafemme. *[see Contraindications (4), Warning and Precautions (5.1), and Use in Specific Populations (8.1, 8.3)]*.

4 Contraindication

BREXAFEMME is contraindicated in:

Pregnancy *[see Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.3)]*

5.1 Risk of Fetal Toxicity

Based on findings from animal studies, BREXAFEMME use is contraindicated in pregnancy because it may cause fetal harm. In animal reproduction studies, ibrexafungerp administered orally to pregnant rabbits during organogenesis was associated with fetal malformations including absent forelimb(s), absent hindpaw, absent ear pinna, and thoracogastroschisis at dose exposures greater or equal to approximately 5 times the human exposure at the recommended human dose.

For females of reproductive potential, verify the patient is not pregnant prior to initiating therapy with BREXAFEMME. Advise females of reproductive potential to use effective contraception

during treatment with BREXAFEMME and for 4 days after last dose [see *Use in Specific Populations* (8.1, 8.3) and *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies, BREXAFEMME use is contraindicated in pregnancy because it may cause fetal harm. In pregnant rabbits, oral ibrexafungerp administered during organogenesis was associated with fetal malformations including absent forelimb(s), absent hindpaw, absent ear pinna, and thoracogastroschisis at dose exposures greater or equal to approximately 5 times the human exposure at the RHD. Oral ibrexafungerp administered to pregnant rats during organogenesis was not associated with fetal toxicity or increased fetal malformations at a dose exposure approximately 5 times the human exposure at the RHD (*see Data*). Available data on BREXAFEMME use in pregnant women are insufficient to draw conclusions about any drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

There is a pregnancy safety study for BREXAFEMME. If BREXAFEMME is inadvertently administered during pregnancy or if pregnancy is detected within 4 days after a patient receives BREXAFEMME, pregnant women exposed to BREXAFEMME and healthcare providers should report pregnancies to SCYNEXIS, Inc. at 1-888-982-SCYX (7299).

Data

Animal Data

Reviewer comment: The Animal Data subheading in approved labeling is not included for purposes of brevity.

8.3 Females and Males of Reproductive Potential

Based on animal data, BREXAFEMME may cause fetal harm when administered to a pregnant female [see *Use in Specific Populations* (8.1)].

Pregnancy Testing

For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment with BREXAFEMME [see *Dosage and Administration* (2.3), *Contraindications* (4) and *Use in Specific Populations* (8.1)].

Contraception

Females

For treatment of VVC, advise females of reproductive potential to use effective contraception during treatment with BREXAFEMME and for 4 days after the last dose.

For reduction in the incidence of RVVC, advise females of reproductive potential to use effective contraception throughout the 6-month treatment period with BREXAFEMME and for 4 days after the last dose.

17 PATIENT COUNSELING INFORMATION

Risk of Fetal Toxicity

BREXAFEMME is contraindicated in pregnancy since it may cause fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*].

Advise patients who have inadvertently taken BREXAFEMME during pregnancy that there is a pregnancy safety study that monitors pregnancy outcomes. Encourage these patients to report their pregnancy to SCYNEXIS, Inc. at 1-888-982-7299 [*see Use in Specific Populations (8.1)*].

For treatment of VVC, advise females of reproductive potential to use effective contraception while taking BREXAFEMME and for 4 days after the last dose.

For reduction in the incidence of RVVC, advise females of reproductive potential to use effective contraception throughout the 6-month treatment period with BREXAFEMME and for 4 days after the last dose [*see Use in Specific Populations (8.3)*].

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/s/

JEAN L LIMPERT
10/07/2022 02:34:49 PM

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10/07/2022 04:43:33 PM

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10/11/2022 02:48:16 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 4, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214900/S-002
Product Name and Strength:	Brexafemme (ibrexafungerp) Tablets, 150 mg
Applicant/Sponsor Name:	Scynexis, Inc. (Scynexis)
OSE RCM #:	2022-1125-1
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

Scynexis submitted revised container label and carton labeling received on September 29, 2022 for Brexafemme. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Brexafemme (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Myers, D. Label and Labeling Review for Brexafemme (NDA 214900/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 AUG 31. RCM No.: 2022-1125.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 29, 2022

Container label



(b) (4)

Carton labeling

(b) (4)



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/s/

DEBORAH E MYERS
10/04/2022 10:14:08 AM

VALERIE S VAUGHAN
10/05/2022 09:36:33 AM

MEMORANDUM

REVIEW OF LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 31, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214900/S-002
Product Name and Strength:	Brexafemme (ibrexafungerp) Tablets, 150 mg
Applicant/Sponsor Name:	Scynexis, Inc. (Scynexis)
OSE RCM #:	2022-1125
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

Scynexis submitted their efficacy supplement on May 31, 2022 for Brexafemme (ibrexafungerp) NDA 214900/S-002 to propose the addition of a new indication for the prevention of recurrent vulvovaginal candidiasis (RVVC). Subsequently, the Division of Anti-Infectives (DAI) requested that we review the proposed prescribing information (PI) for Brexafemme (Appendix A) for areas of vulnerability that may lead to medication errors.

2 BACKGROUND/REGULATORY HISTORY

NDA 214900 was approved on June 1, 2021 for the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis (VVC), at a dosage of 300 mg (two 150 mg tablets) administered approximately 12 hours apart (e.g., in the morning and in the evening) for one day, for a total daily dosage of 600 mg (four 150 mg tablets).

On May 31, 2022, Scynexis submitted their efficacy supplement to propose the addition of a new indication for the prevention of RVVC, at a dosage of 300 mg (two tablets of 150 mg) administered approximately 12 hours apart (e.g., in the morning and in the evening) for one day, for a total daily dosage of 600 mg (four 150 mg tablets) monthly for six months.

3 CONCLUSION AND RECOMMENDATIONS

As part of their submission, the Applicant stated their intent to market and distribute Brexafemme for the new indication (b) (4) using the same National Drug Code (NDC) number approved under the original NDA. Thus, as part of our overall assessment, we reviewed the current in-use container labels and carton labeling to determine if there are areas of vulnerability to medication error in light of proposed changes to the PI.

The proposed prescribing information, container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and Section 5 for the Applicant.

4 RECOMMEDATIONS FOR DIVISION OF ANTI-INFECTIVES (DAI)

Table 1. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information (HPI)			
1.	As currently presented under the <i>Dosage and Administration</i> section, the frequency of dosing for treatment of VVC is inconsistent with the frequency of dosing stated in subsection 2.1 of the Full Prescribing Information (FPI). The HPI states "...twice a day..." while subsection 2.1 of the FPI states "...administered approximately 12 hours apart (e.g., in the morning and in the evening)...". Additionally, the text for the indication for VVC in Highlights under the header <i>Dosage and Administration</i> lacks the	The recommended dosage statement terminology should be consistent across the labeling to mitigate risk of confusion and medication errors.	To provide consistent dosage statements throughout the PI, revise the recommended dosage statement for treatment of VVC under the <i>Dosage and Administration</i> section of the HPI to match the recommended dosage statement for treatment of VVC in the FPI. revise the current text "...twice a day..." to "...administered approximately 12 hours apart (e.g., in the morning and in the evening)...") and following the text "600 mg" add the text "(four 150 mg tablets)."

Table 1. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	text “...(four 150 mg tablets).” included in subsection 2.1 <i>Recommended Dosage</i> .		

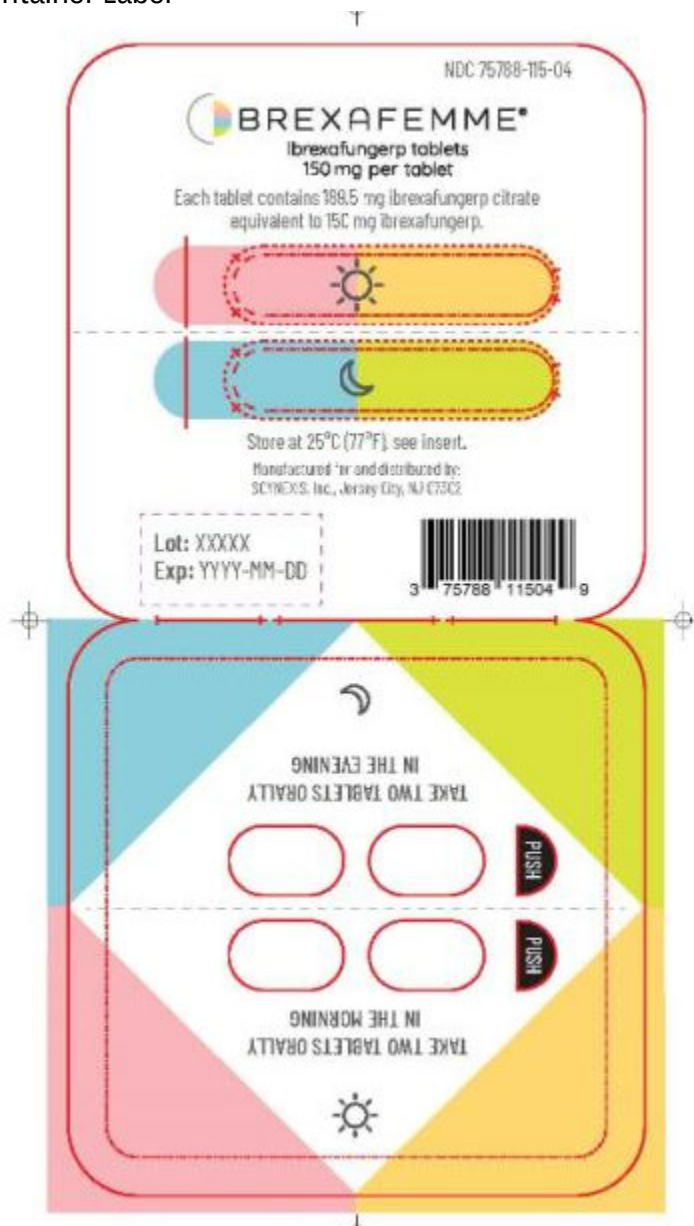
5 RECOMMENDATIONS FOR SCYNEXIS, INC

Table 2. Identified Issues and Recommendations for Scynexis, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	As currently presented, the in-use container label includes the text “Take two tablets orally in the morning” and “Take two tablets orally in the evening” without mention of the amount of time to separate the doses.	The Prescribing Information states to administer the doses “approximately 12 hours apart.” Inconsistent dosage information across the labels and labeling could result in administration errors.	Revise the container label to incorporate the timing of dose administration. For example: “Take doses approximately 12 hours apart” “Take two tablets orally in the morning” “Take two tablets orally in the evening”
2.	As currently presented, the storage statement on the container label “Store at 25°C(77°F)” is inconsistent with the storage statement within the labeling because it only includes the upper temperature of the temperature range.	Inconsistent storage statements could result in storage errors and administration of deteriorated drug product.	Revise the storage statement on the container label to include the temperature range, for example, revise to: “Store at room temperature between 20°C to 25°C (68°F to 77°F).”
Carton Labeling			
1.	The “usual dosage” statement, “the recommended dosage of BREXAFEMME is 300 mg	With this supplement, a new “monthly for six months” duration is proposed for the treatment	Revise the “usual dosage” statement to: “Recommended dosage: See Prescribing Information.”

Table 2. Identified Issues and Recommendations for Scynexis, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(two tablets of 150 mg) taken orally, twice a day, for one day,” does not align with the Prescribing Information.	of RVVC. As proposed, the current “usual dosage” statement could lead to confusion and result in administration errors due to differences in dosage regimen duration.	

APPENDIX A. IMAGES OF LABEL AND LABELING REVIEWED

- Prescribing Information (PI) (Images not shown):
 - o Clean proposed (Draft) PI received on June 23, 2022, available at the following link: <\\CDSESUB1\evsprod\nda214900\0040\m1\us\draft-plr-label-rvvc-supplement.doc>.
 - o Tracked changes PI received on July 6, 2022, available at the following link: <\\CDSESUB1\evsprod\nda214900\0041\m1\us\draft-plr-label-rvvc-supplement-track-changes.doc>.
- Current In-Use Container Label and Carton Labeling, retrieved on August 3, 2022
 - o Container Label



o Carton Labeling



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/s/

DEBORAH E MYERS
08/31/2022 02:14:52 PM

VALERIE S VAUGHAN
08/31/2022 02:46:28 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214900Orig1s002

**Risk Assessment and Risk Mitigation
Review(s)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214900 – Supplement 002
PDUFA Goal Date	November 30, 2022
OSE RCM #	2022-2695
Team Leader	Naomi Boston, Pharm.D.
Associate Director for REMS Design and Evaluation	Laura Zendel, Pharm.D., BCPS
Review Completion Date	November 29, 2022
Subject	Evaluation of Need for a REMS
Established Name	Ibrexafungerp
Trade Name	Brexafemme
Name of Applicant	Scynexis, Inc
Therapeutic Class	Triterpenoid antifungal
Dosing Regimen	300 mg (two 150 mg tablets) orally taken 12 hours apart for one day, for a total daily dosage of 600 mg monthly for 6 months

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Brexafemme (ibrexafungerp) is necessary to ensure the benefits outweigh its risks. Ibrexafungerp was originally approved on June 1, 2021, for the treatment of vulvovaginal candidiasis (VVC) in adult and post-menarchal pediatric females. On May 31, 2022, Scynexis, Inc (the Applicant) submitted a supplement (S-002) to its New Drug Application (NDA) 214900 for ibrexafungerp with the proposed indication for the prevention of recurrent vulvovaginal candidiasis (RVVC). The FDA approved indication will be for reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC) in adult and post-menarchal pediatric females. This application is under review in the Division of Anti-infectives (DAI). The risk of concern with ibrexafungerp is the potential for embryofetal toxicity based on animal data seen in pregnant rabbits resulting in fetal malformations including absent forelimb(s), absent hindpaw, absent ear pinna and thoracogastroschisis at doses greater or equal to approximately five times the recommended human dose (RHD). The applicant did not submit a proposed REMS or risk management plan with this application.

In the original approval of ibrexafungerp, embryofetal toxicity was listed as a warning and precaution based on nonclinical data. There have been no new safety information for ibrexafungerp since the time of approval. However, with the introduction of the longer treatment duration of monthly for 6 months for the RVVC indication, DAI determined that highlighting this information in a boxed warning to increase visibility of this risk is essential. The prescribing information will include a boxed warning for the risk of embryofetal toxicity, instructing prescribers to verify that the patient is not pregnant prior to initiating ibrexafungerp treatment, and to reassess pregnancy status prior to each dose when used monthly for 6 months for RVVC. It is also advised that females of reproductive potential use effective contraception during treatment of VVC and throughout the 6-month treatment period for RVVC and for 4 days after the last dose. The prescribing information will include a medication guide, and the Applicant has stated that a Dear Health Care Provider Letter will be sent to potential prescribers of ibrexafungerp outlining the information in the boxed warning. Furthermore, the Applicant will continue to maintain the pregnancy registry for any reports of pregnancies or for patients who may have taken ibrexafungerp inadvertently prior to learning of their pregnancy status. In addition, there is a planned post-marketing pregnancy safety study in females exposed to ibrexafungerp to provide clinically relevant human safety data intended to inform healthcare providers caring for females of reproductive potential in the future.

DRM agrees with the risk mitigation measures outlined above and have determined that a REMS is not necessary to ensure the benefits of ibrexafungerp outweigh its risks. Due to the limited evidence of the risk in one animal species, the updated labeling is sufficient to communicate the risk and appropriate risk mitigation recommendations. If additional safety information becomes available, DRM may re-evaluate this recommendation.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Brexafemme (ibrexafungerp) is necessary to ensure the benefits outweigh its risks. Ibrexafungerp was originally approved on June 1, 2021, for the treatment of VVC. On May 31, 2022, Scynexis, Inc submitted an efficacy supplement (S-002) for ibrexafungerp with the proposed indication for the prevention of recurrent vulvovaginal candidiasis (RVVC). The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Ibrexafungerp is a first in class triterpenoid antifungal drug that inhibits glucan synthase, an enzyme involved in the formation of 1,3- β -D-glucan – an essential component of the fungal cell wall.¹ It demonstrates concentration-dependent fungicidal activity against *Candida* species and retains activity to against most fluconazole resistant *Candida* species. The half-life is 20 hours. Ibrexafungerp was originally approved by the FDA on June 1, 2021, as an oral, one day 300 mg dose administered 12hours apart (total dose 600mg) for the treatment of adult and post-menarchal pediatric females with VVC.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 214900/S-002 relevant to this review:

- 06/01/2021: Brexafemme (ibrexafungerp tablets) approved for the treatment of vulvovaginal candidiasis in adult and post-menarchal pediatric females.
- 05/31/2022: Supplement 002 for NDA 214900 received for the proposed indication of treatment of prevention of recurrent vulvovaginal candidiasis.
- 11/23/2022: The Agency issued labeling comments to the applicant reiterating the need for a boxed warning and adding language to recommend reassessment of pregnancy status prior to each dose.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

RVVC is defined as having three to four or more episodes of VVC within a 12-month period. Vaginal symptoms such as vulvar erythema and pruritis, odor, cheese-like or watery vaginal discharge and the presence of yeast are often present in this condition, however, the patient may also be asymptomatic.^{2,a} *Candida albicans* accounts for 85-90% of cases, with the remainder attributed to

^a Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

other species of *Candida* such as *C. glabrata*, *C. krusei*, *C. famata*, and *C. tropicalis*.² These infections are typically rare before menarche, peaks during reproductive years and then declines after menopause. Risk factors may include contraceptive use, antibiotic use, sexual activity, and diabetes.³ It is estimated that 75% of women will have at least one episode of VVC in their lifetime, and 40%-45% will have two or more episodes.⁴ VVC is frequently self-diagnosed or empirically diagnosed by healthcare providers. It has been reported to affect nearly 6 million women in the United States each year, with nearly 325,000 women experiencing RVVC annually.^{2,3} Treatment has been estimated to be \$374 million in direct medical costs related to treat these conditions each year.^{2,3,b} RVVC can adversely affect a woman's quality of life, relationships, mental health and sexual activity. Nearly 80% of women in qualitative interview of 127 women with RVVC in the United States reported that the condition affected their personal lives including the ability to socialize and exercise and half reported fear of social interaction and dating. Approximately 40% of these women considered RVVC a significant burden on their lives, with the most extreme burdens being discomfort from symptoms, avoidance of sexual activity, and out-of-pocket costs due to prescription or over the counter drugs and office visit copays.²

3.2. Description of Current Treatment Options

The pathogenesis of RVVC is poorly understood, and many women have no predisposing or underlying conditions. Suppressive maintenance therapies are effective for controlling RVVC but are rarely curative long-term.⁴ For RVVC infections caused by *C. albicans*, topical azole therapies such as over the counter clotrimazole, miconazole, or tioconazole creams and/or vaginal suppositories may be effective. While not FDA approved for RVVC, guidelines from the CDC for sexually transmitted infections for VVC recommend oral therapy with fluconazole 100 mg, 150mg or 200 mg every third day for a total of three doses to attempt mycologic remission before initiating a maintenance antifungal regimen. Oral fluconazole at doses of either 100 mg, 150 mg, or 200 mg weekly for 6 months is the recommended maintenance regimen for RVVC per these guidelines.⁴ Fluconazole resistance has been increasing and making treatment of RVVC challenging. In addition, *C. glabrata* and other non *Candida albicans* species have been observed in 10%-20% of women with RVVC, which makes treatment with conventional antimycotic therapies difficult.^{3,4} Vivjoa (oteseconazole), approved on April 28, 2022, is currently the only FDA approved treatment for RVVC. Vivjoa is indicated to reduce the incidence of RVVC in females with a history of RVVC who are not of reproductive potential.⁵ None of the products currently used in the treatment of RVVC have been approved with a REMS.

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

4. Benefit Assessment

SCY-078-304, NCT04029116, was a Phase 3, randomized, placebo-controlled clinical trial conducted in 260 patients to evaluate the safety and efficacy of ibrexafungerp administered as 300 mg (two 150 mg tablets) 12 hours apart for one day, for a total daily dosage of 600 mg administered once monthly for six months for reduction in the incidence of RVVC. This was a global, multi-regional trial, with 33% of the participants coming from the United States, 28% from Bulgaria, 28% from Russia, and 12% from Poland.¹ Inclusion criteria were non-pregnant post-menarchal females presenting with a symptomatic VVC episode, and a history of RVVC defined as at least 3 episodes of VVC in the previous 12 months. Patients were randomized 1:1 to receive ibrexafungerp (n = 130) or placebo (n = 130) administered as a single-day treatment repeated every four weeks for a total of six single-day treatments. Efficacy was assessed as the percentage of patients with clinical success, which was defined as patients with no proven culture indicative of RVVC, or presumed or suspected RVVC requiring antifungal therapy up to test of cure (TOC) at week 24. Clinical success was also assessed at the week 36 follow-up visit.

Clinical success was statistically significantly greater in patients who received ibrexafungerp compared to the placebo group. The clinical success rate of TOC was lower for patients who received ibrexafungerp in the United States compared to ex-United States (ex-US) sites. In all regions the ibrexafungerp group had higher rates of clinical success compared to placebo: United States 33% vs 23% and ex-US: 81% vs 68% in the ibrexafungerp vs placebo arms, respectively.

An overview of the efficacy results for ibrexafungerp compared to placebo in SCY-078-304 are presented in Table 1 below.

Table 1: Clinical and Mycological Response in Post-menarchal Females with RVVC in SCY-078-304, ITT Population¹

	SCY-078-304		
	Ibrexafungerp N = 130 n (%)	Placebo N = 130 n (%)	Difference (95% CI) P-value
Clinical success at TOC (Week 24)	85 (65.4)	69 (53.1)	12.7 (2.2, 23.1) 0.020
Reasons For Clinical Failure at TOC			
Mycologically Proven Recurrence	30 (23.1)	47 (36.2)	
Presumed Recurrence	7 (5.4)	3 (2.3)	
Suspected Recurrence	2 (1.5)	4 (3.1)	
Imputed Recurrence ¹	6 (4.6)	7 (5.4)	
Clinical success at Week 36 Follow Up Visit	75 (57.7)	60 (46.2)	11.9 (1.1, 22.6) 0.034
Reasons For Clinical Failure at Week-36 Follow-up Visit			
Mycologically Proven Recurrence	37 (28.5)	51 (39.2)	

Presumed Recurrence	8 (6.2)	5 (3.8)	
Suspected Recurrence	4 (3.1)	5 (3.8)	
Imputed Recurrence ¹	6 (4.6)	9 (6.9)	

Based on the data above, the review division recommends approval of ibrexafungerp for reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC) in adult and post-menarchal pediatric females.^c

5. Risk Assessment & Safe-Use Conditions

The risk of concern for ibrexafungerp is the potential of embryo-fetal toxicity, based on non-clinical data.^d A description of the potential risk for embryo-fetal toxicity is described below.

5.1. Embryofetal Toxicity

When administered to pregnant rabbits, ibrexafungerp was associated with fetal malformations including absent forelimb(s), absent hindpaw, absent ear pinna and thoracogastroschisis at doses greater or equal to approximately five times the recommended human dose (RHD).¹ Malformations including absent hind paw and anencephaly occurred with an increased litter incidence in rabbits exposed to a higher dose, approximately 13 times RHD. In a rat embryo-fetal study, no fetal malformations or changes in embryo-fetal survival or fetal body weights occurred with any doses of ibrexafungerp. These non-clinical data were reviewed in the original submission of ibrexafungerp and was labeled as a contraindication and placed in the warnings and precautions section in the prescribing information at the time of approval.⁶

The clinical trial protocol for study SCY-078-304 specified specific inclusion criteria for subjects of reproductive potential including that they must continue using effective contraception defined as an IUD, implant, oral contraceptive, or patch starting 30 days prior to baseline and use a non-hormonal barrier method, the male partner has a vasectomy at least 3 months prior to baseline, use of a barrier method (male or female condom or diaphragm), or abstinence. Topical contraceptives such as spermicides and vaginal ring were not considered acceptable forms of contraceptive for the study. The patients agreed to continue their contraceptive method during treatment until 10 days post-treatment. Additionally, a urine pregnancy test was performed at baseline (day 1) and at unscheduled visits if needed by the local laboratory for all subjects of reproductive potential. The

^c Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

^d Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

subject must have a negative pregnancy test before taking the first dose of study drug. Subjects self-administered study drug at home.

Although pregnant patients were excluded from SCY-078-304, four patients became pregnant during the study, one of whom was treated with ibrexafungerp. Two subjects were in the placebo arm and one subject became pregnant prior to randomization of treatment. The subject who became pregnant while on ibrexafungerp was a 37-year-old female. She received three 150 mg doses of fluconazole followed by two 300 mg doses of ibrexafungerp at baseline, week 4, and week 8 of the study (last dose of ibrexafungerp given on day 59). Concomitant medications also included levonorgestrel. The subject reported pregnancy on day 79 and was subsequently withdrawn from the study. The subject had a normal pregnancy and delivered a healthy newborn.⁷

Because the RVVC indication requires a longer duration of therapy (six months) compared to the original VVC indication (2 doses spaced 12 hours apart for 1 day), DAI determined elevation of the risk of embryofetal toxicity to a boxed warning was necessary to increase the visibility of the risk and the need for appropriate mitigation measures.

6. Expected Postmarket Use

Ibrexafungerp is likely to be used in an outpatient, ambulatory care setting and may be prescribed by a wide variety of healthcare providers, including gynecologists and obstetricians, family medicine practitioners, and mid-level providers such as physician assistants or nurse practitioners. It is expected that these providers will have knowledge in counseling patients on preventive contraceptive measures and the need to reassess pregnancy status while taking ibrexafungerp.

7. Risk Management Activities Proposed by the Applicant

The Applicant developed a pregnancy registry at the original time of approval for patients who may be exposed to ibrexafungerp during pregnancy. Recommendations are to report any pregnancies to women who may have inadvertently taken ibrexafungerp during pregnancy, or if pregnancy is detected within four days after a patient received this drug to the Applicant's pregnancy registry. Contact information for this registry is outlined in the prescribing information in warnings and precautions.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of ibrexafungerp based on the efficacy and safety information currently available.

RVVC is a condition that can adversely affect a woman's quality of life physically, emotionally, and financially. Suppressive maintenance therapies are effective for controlling RVVC, but there is no cure. In the trial for the treatment of RVCC, ibrexafungerp achieved statistically significant clinical success in patients who received ibrexafungerp compared to the placebo group (65.4% versus 53.1%, p value <0.020).

The risk of concern with ibrexafungerp is the potential for embryofetal toxicity based on animal data seen in pregnant rabbits resulting in fetal malformations including absent forelimb(s), absent hindpaw, absent ear pinna and thoracogastroschisis at doses greater or equal to approximately five times the RHD. Malformations including absent hind paw and anencephaly occurred with an increased litter incidence in rabbits exposed to a higher dose, approximately 13 times RHD.

The potential for embryofetal toxicity based on nonclinical data is not a new risk for therapies used for the treatment of VVC and/or RVVC. Though not FDA approved for the treatment of RVVC, fluconazole is recommended in treatment guidelines⁴ as maintenance therapy for RVVC in doses up to 200 mg weekly for six months. The potential for fetal harm is discussed in the Diflucan (fluconazole) prescribing information⁸ based on animal data and some case reports of congenital anomalies observed in infants. Dystocia and prolongation of parturition were observed in a perinatal study in rats given 5mg/kg, 20mg/kg and 40mg/kg (approximately 5 to 15 times the RHD). Delays in ossification were observed in the fetus of pregnant rats given doses of 25mg/kg and higher doses. At doses ranging from 80 to 320 mg/kg (approximately 2 to 8 times the 400 mg clinical dose based on body surface area), embryoletality in rats was increased and fetal abnormalities such as wavy ribs, cleft palate and abnormal craniofacial ossification were observed. The prescribing information also states that there have been a few published case reports of similar congenital anomalies in infants exposed in utero to high doses of fluconazole (400 to 800 mg per day) during most, or the entire first trimester. These anomalies include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.⁷ Recommendations in the prescribing information advise effective contraceptive measures should be considered in women of child-bearing potential who are being treated with fluconazole 400 to 800 mg/day and should continue throughout the treatment period and for approximately one week after the final dose.

In April 2022, Vivjoa (oteseconazole) was the first drug FDA approved to reduce the incidence of RVVC, specifically in females with a history of RVVC who are not of reproductive potential. This drug is contraindicated in females of reproductive potential and in pregnant and lactating women because of potential risks to a fetus or breastfed infant based on animal studies, and the drug's prolonged half-life. Females who are not of reproductive potential are defined in oteseconazole's prescribing information⁵ as persons who are biological females who are postmenopausal or have another reason for permanent infertility (e.g., tubal ligation, hysterectomy, salpingo-oophorectomy). Ocular abnormalities such as cataracts, opacities, exophthalmos/buphthalmos, optic nerve/retinal atrophy, lens degeneration and hemorrhage were observed in the offspring of pregnant rats dosed at 7.5 mg/kg/day (approximately 3.5 times the RHD seen in patients treated for RVVC).⁵ Oteseconazole's long drug exposure window (690 days – based on 5 times the half-life of 138 days) precludes adequate mitigation of the embryofetal toxicity risks.

Ibrexafungerp will be the first antifungal approved for the treatment of RVVC in females of reproductive potential. Embryofetal toxicity was listed as a warning and precaution at the time of original approval based on nonclinical data and the indication being VVC and a short course of therapy. With the introduction of the longer treatment duration of monthly for 6 months for the RVVC indication,

inadvertent exposure during pregnancy is increased compared to the acute VVC indication. To further mitigate this risk, the review team determined that highlighting this information in a boxed warning to increase visibility of this risk is essential. In addition, the prescribing information will include a medication guide, and the Applicant has stated that a Dear Health Care Provider Letter will be sent to potential prescribers of ibrexafungerp outlining the information in the boxed warning.

Given the wide variety of health care providers that may prescribe ibrexafungerp and the large numbers of patients of reproductive potential that may be potentially exposed to ibrexafungerp for the treatment of RVVC, DRM considered whether there would be a need for additional risk mitigation beyond labeling. DRM met with members of DAI and the Department of Pediatric and Maternal Health (DPMH) to discuss labeling of embryofetal toxicity in a box warning as well as other risk mitigation measures proposed by the Applicant. DRM agreed with DAI and DPMH's proposed labeling changes to include a BW and recommendations to check pregnancy status prior to starting treatment and for patients to continue contraceptives throughout treatment and for 4 days following treatment. However, based on the patient population likely to receive this product and the intermittent dosing once a month for a short duration of treatment, DRM did not agree that these strategies were sufficient to mitigate the risk. DRM recommended including additional recommendations to check the pregnancy status prior to each dose in the labeling. Pregnancy testing prior to each dose is low burden and more impactful for mitigating the risk of embryo-fetal toxicity by ruling out pregnancy prior to each dose. Given the relatively short half-life compared to fluconazole and oteseconazole, if pregnancy can be excluded prior to each monthly dose, the chance of a pregnancy exposure to ibrexafungerp would be low. The review team agreed to include language in the Prescribing Information and Medication Guide to recommend reassessment of pregnancy status prior to each dose. DRM determined a REMS is not necessary for the approval of the RVVC indication of ibrexafungerp. It is expected that robust labeling will be sufficient to inform likely health care providers who can counsel patients on pregnancy prevention and the potential risks that might occur with the use of ibrexafungerp. Due to the limited evidence of the risk in one animal species, the updated labeling is sufficient to communicate the risk and appropriate risk mitigation recommendations.

The prescribing information will include a boxed warning for the risk of embryofetal toxicity, instructing prescribers to verify that the patient is not pregnant prior to initiating ibrexafungerp treatment, and reassessing pregnancy status prior to each dose when used monthly for 6 months for RVVC. It is also advised that females of reproductive potential use effective contraception during treatment of VVC and throughout the 6-month treatment period for RVVC and for 4 days after the last dose. Furthermore, the Applicant will continue to maintain the pregnancy registry for any reports of pregnancies or for patients who may have taken ibrexafungerp inadvertently prior to learning of their pregnancy status. There is also a planned post-marketing pregnancy safety study in females exposed to ibrexafungerp. The goal of the study is to provide clinically relevant human safety data that can inform healthcare providers treating or counseling patients who are pregnant or anticipating pregnancy about the safety of ibrexafungerp through inclusion of the information in the prescribing information. DRM agrees with the measures outlined above as measures to mitigate the potential risk for embryofetal toxicity in this patient population.

9. Conclusion & Recommendations

DRM determined a REMS is not necessary for ibrexafungerp to ensure the benefits outweigh the risks. The management of the risk of embryofetal toxicity associated with ibrexafungerp can be communicated through labeling. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. References

¹ Draft prescribing information, Ibrexafungerp (Brexafemme) FDA comments November 21, 2022

² Blostein F et al. Recurrent vulvovaginal candidiasis. *Annals of Epidemiology*. Vol 27(9), September 2017, pgs 575-582

³ Bénédict K et al. Survey of incidence, lifetime prevalence, and treatment of self-reported vulvovaginal candidiasis, United States, 2020. *BMC Womens Health*. 2022; 22: 147.

⁴ Sexually Transmitted Infections Treatment Guidelines, 2021 – Vulvovaginal Candidiasis
www.cdc.gov/std/treatment-guidelines/candidiasis.htm accessed November 23, 2022

⁵ Vivjoa (oteseconazole capsules) Prescribing Information. Mycovia Pharmaceuticals, Inc. Durham, NC 27703. April 2022

⁶ Brexafemme (ibrexafungerp tablets) Prescribing Information. Scynexis, Inc. Jersey City, NJ. June 2021

⁷ Applicant's submission for NDA 214900, Scy0078-304 Study report, pages 194-198

⁸ Diflucan (fluconazole) prescribing information. Pfizer, Distributed by Roerig, New York, NY. March 2022

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