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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Nonclinical Reviewer	James Wild, PhD
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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

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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

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

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

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 ≥ 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

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
Analysis of Condition	• 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. *C. albicans* accounts for 85 to 95% of all *Candida* 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.
Current Treatment Options	• 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.

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 *C. glabrata* or other non-albicans *Candida* 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.
Benefit	• 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. *

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• 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 ≥ 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].

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
		X	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		X	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

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[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 options[13]. The CDC guidelines[2] 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, Mummaw 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. guillermondi, C. kefyr, C. lusitaniae, C. nevariensis, C. parapsilosis* and *C. tropicalis*. In addition, 3 subjects presented with *Saccharomyces cervesiae* 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. dubliniensis* 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								
Candida albicans	120	0.015 - 0.25	0.06	0.12	122	0.015 - 0.25	0.06	0.12
Candida dubliniensis	2	0.06 - 0.25	--	--	2	0.12 - 0.5	--	--
Candida fermentati	1	0.25	--	--	0	--	--	--
Candida glabrata	6	0.25 - 1	0.5	1	5	0.25 - 0.5	0.25	0.5

Candida spp. at screening, n (%)	Ibrexafungerp (N = 130)				Placebo (N = 130)			
	N	Range	MIC50	MIC90	N	Range	MIC50	MIC90
Candida guilliermondii	0	--	--	--	1	2	--	--
Candidda kefyr	2	0.06 - 0.25	--	--	0	--	--	--
Candida lusitaniae	0	--	--	--	1	4	--	--
Candida nivariensis	1	0.5	--	--	0	--	--	--
Candida parapsilosis	1	0.5	--	--	0	--	--	--
Candida tropicalis	0	--	--	--	1	0.25	--	--
Saccharomyces cervisiae	1	0.5	--	--	2	1	--	--
At baseline								
Candida albicans	11	0.03 – 0.12	0.06	0.12	19	0.03 – 0.25	0.06	0.12
Candida glabrata	4	0.25 – 0.5	0.5	0.5	3	0.25 – 1	0.25	1
Candida parapsilosis	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** 20 mg/kg/day: 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. 40 mg/kg/day: 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. 80 mg/kg/day: 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. Accumulation: Day 182 AUC values were approximately 2-fold higher than Day 1 AUC values consistent with plasma accumulation of SCY-078. Dose proportionality: 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)** 30 mg/kg/day: $t_{1/2}$ = 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. 60 mg/kg/day: 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. 100 mg/kg/day: 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. Plasma $t_{1/2}$: On Day 1, $t_{1/2}$ values ranged from 7.44 to 8.42 hours for all sexes and doses. Accumulation: 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. Dose proportionality: Overall, plasma C_{max} and AUC values for SCY-078 increased in a less than dose-proportional manner.

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

	Frequency: once per day
Route of administration:	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)
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

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)

FD – Found Dead; UE – Unscheduled Euthanasia.

	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** HD males: +130% WBC***; +549% neutrophils***; +142% percent neutrophils***; +98% monocytes***; +33% percent monocytes*; +21% platelets***; -36% percent lymphocytes***; -82% percent eosinophils*** MD females: +72% percent neutrophils**; +16% platelets*** HD Females: +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.

Clinical Chemistry *: p ≤ 0.05 **: p ≤ 0.01 ***: p ≤ 0.001 AST = aspartate aminotransferase ALT = alanine aminotransferase ALP = alkaline phosphatase	**End of Dosing** LD Males: +82% ALT* MD Males: +51% AST***; +74% ALT***; -58% 12-week triglyceride***; -5.5% total protein*; -7.4% albumin*** HD Males: +97% AST***; +117% ALT***; +122% ALP**; -41% cholesterol***; -59% triglyceride***; -7% total protein*; -22% albumin***; -30% albumin/globulin ratio***. MD Females: -67% triglyceride***; -5% total protein* HD Females: +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** Adrenal Gland: 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. Ovary: Relative ovary weights (relative to brain weight) were significantly increased approximately 20% compared to control values with no histological correlates. Thymus: 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. Liver: 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. Pituitary: pituitary weights (absolute and relative to brain weight) were significantly reduced in MD (21%-22%) and HD (29%) females with no histological correlates. Prostate: Prostate weights (absolute and relative to brain weight) were significantly decreased in HD males (20%-22%) compared to control values with no histological correlates.

	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 deceases 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.

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.

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. Testes: 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. Kidney: 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. Liver: 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 Thymus: 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. Uterus: 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. Spleen: 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** Lung: 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. GI Tract: 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. Lymphoid organs: 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. Liver and Gall Bladder: 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. Epididymides: 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.

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/m^2 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 ≥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/m^2)			
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)
Candida albicans	11 (8.5)	19 (14.6)	30 (11.5)
Candida glabrata	4 (3.1)	3 (2.3)	7 (2.7)
Candida parapsilosis	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 11for 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	Ibrexafungerp 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)

	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

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 (Derogastis 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.

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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 Treatment [20], 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 use [21] 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 ≥ 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 ±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 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/N_s (%)	**Placebo N=130 n/N_s (%)**	**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

	Adverse Events	
System Organ Class (SOC) Preferred Term	**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 ≥ 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] Jaquiery, 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** ***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**
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.*		

ADVERSE REACTIONS	The most frequent adverse reactions (≥ 2%) reported (b) (4) ere diarrhea, nausea, abdominal pain, dizziness, and vomiting. (6.1)	• Treatment of VVC: The most frequent adverse reactions (incidence ≥ 2%) reported were diarrhea, nausea, abdominal pain, dizziness and vomiting. (6.1) • Reduction in the incidence of RVVC: 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).

<table>
<tr><td></td><td>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)].</td><td>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)].</td></tr>
<tr><td colspan="3">Reviewer's Comments: The sentence is rephrased for clarity.</td></tr>
<tr><td>Section: 6
ADVERSE REACTIONS

Subsection 6.1 Clinical Trials Experience (FPI)</td><td>Subsection 6.1: Clinical Trials Experience
Table 2. Adverse Reactions with Rates ≥2% in BREXAFEMME-Treated Patients
<table><tr><th>Adverse Reaction</th><th>BREXAFEMME
N = 130
n (%)</th><th>Placebo
N = 130
n (%)</th></tr><tr><td>Abdominal pain[1]</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>Headache[2]</td><td colspan="2">(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><tr><td colspan="3">(b) (4)</td></tr></table></td><td>Subsection 6.1: Clinical Trials Experience
Table 2. Adverse Reactions with Rates ≥2% in BREXAFEMME-Treated Patients
<table><tr><th>Adverse Reaction[1]</th><th>BREXAFEMME
N = 130
n (%)</th><th>Placebo
N = 130
n (%)</th></tr><tr><td>Headache</td><td>23 (17.6)</td><td>10 (7.6)</td></tr><tr><td>Abdominal pain[2]</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></td><td>7 (5.4)</td><td>5 (3.8)</td></tr><tr><td>Nausea</td><td>5 (3.8)</td><td>1(0.8)</td></tr><tr><td>Urinary tract infection</td><td>4 (3.1)</td><td>0</td></tr><tr><td>Fatigue</td><td></td><td></td></tr></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</td></tr>
<tr><td colspan="3">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.</td></tr>
<tr><td>Section: 8
USE IN SPECIFIC POPULATIONS</td><td>8.3 Females and Males of Reproductive Potential

<u>Contraception</u>

Females

Advise females of reproductive potential to use effective contraception during treatment with BREXAFEMME and for 4 days after the last dose.</td><td>8.3 Females and Males of Reproductive Potential

<u>Contraception</u>

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</td></tr>
</table>

		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.

Table 5. Clinical and Mycological Response, ITT Population

	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)		

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

(b) (4)

Note: Subjects not meeting the definition of clinical success were considered clinical failure.

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

	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	30 (23.1)	47 (36.2)	
Mycologically Proven 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	37 (28.5)	51 (39.2)	
Mycologically Proven 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			

Abbreviations: CI = confidence interval; TOC = test of cure.
Note: Subjects not meeting the definition of clinical success were considered clinical failure.

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. *[see Clinical Pharmacology (12.3)].*
Section: 12 CLINICAL PHARMACOLOGY Subsection 12.3 Pharmacokinetics		Specific Populations *Post-Menarchal Pediatric Females and Geriatric Patients* 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). *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.

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: 49		
Number of investigators who are Sponsor employees (including both full-time and part-time		

employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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)

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/

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

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